Developing A Chinese Medicine Syndrome Differentiation Questionnaire For Chronic Pain Patients Who Use Opioid Medications

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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DECLARATION

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and, ethics procedures and guidelines have been followed.

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PUBLICATIONS

Published manuscripts relevant to the thesis

Xue CC, Helme RD, Gibson S, Hogg M, Arnold C, Somogyi AA, Da Costa C, Wang Y, Lu SC, Zheng Z., *Effect of electroacupuncture on opioid consumption in patients with chronic musculoskeletal pain: protocol of a randomised controlled trial.* Trials, 2012. 13: p. 169.

Published manuscripts outside of the thesis

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May BH, Feng M, Zhou IW, Chang SY, Lu SC, Zhang AL, Guo XF, Lu CJ, Xue CC. *Memory Impairment, Dementia, and Alzheimer's Disease in Classical and Contemporary Traditional Chinese Medicine.* J Altern Complement Med, 2016. 22(9): p. 695-705.

Conference proceeding

Lu, S., Zheng, Z. and Xue, C. (2011). *Musculoskeletal pain and its comorbidities and symptomatology: a systematic review.* In: *The Frontiers of Pain*. Darwin: Australia Pain Society, p.118.

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Manuscript in preparation

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ABREVIATIONS

ADD	Attention deficit disorder
ADHD	Attention deficit hyperactive disorder
AHRQ	Agency for Healthcare Research and Quality
ANOVA	Analysis of variance
AUD	Australian dollar
BDI	Beck Depression Inventory
BT	Behavioural therapy
CBT	Cognitive behavioural therapy
CI	Confidence interval
CIDI	Composite international diagnostic interview
CM	Chinese medicine
CMP	Chronic musculoskeletal pain
CMPQ	Chinese medicine pain questionnaire
EA	Electro acupuncture
EAOM trial	Electroacupuncture on opioid consumption by patients with chronic musculoskeletal pain a randomised controlled trial
GAD	General anxiety disorder
GP	General practitioner
HAM-D	Hamilton rating scale for depression
HREC	Human research ethics committee
KMO	Kaiser–Meyer–Olkin measure
LBP	Low back pain
MANOVA	Multivariate analysis of variance
MDD	Major depressive disorder
MIDAS	Migraine Disability Assessment Questionnaire
MPM	Multidisciplinary pain management
MPQ	McGill Pain Questionnaire
MQS	Medication Quantification Scale version
NOS	Newcastle Ottawa Scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OM	Opioid medication
OR	Odds ratio
PHQ	Patient Health Questionnaire
PMM	Pain and medication management
PMQ	Pain Medication Questionnaire
PPR	Prevalence proportion ratio
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PTSD	Post traumatic stress disorder
QoL	Quality of life
RA	Rheumatoid arthritis
RCMRG	Traditional Chinese Medicine Research Group
RCT	Randomised controlled trial
REA	Real electro acupuncture
RMDQ	Roland Morris Disability Questionnaire
SE	Standard error
SEA	Sham electro acupuncture
SEK	Swedish Krona
SF12	Medical Outcome Short Form Health Survey 12 items

SF36	Medical outcome short form health survey 36 items
SP	Spinal pain
SPSS	Statistical Package for Social Science
SR	Systematic review
TMD	Temporal mandibular joint disorder
UC	Usual care
VAS	Visual analogue scale
WHO	World Health Organization
WHOQOL-BREF	World Health Organization Quality of Life

SUMMARY

Chronic musculoskeletal pain (CMP), characterised by pain in the muscle and joints for more than three months, affects one in five people in Australia and internationally. Chronic musculoskeletal pain is associated with reduced quality of life, loss of productivity, and increased health expenditures to the patients and the society. Chronic musculoskeletal pain is accompanied with comorbidities and accompanying symptoms. Comorbidities increase the burden to health management and deteriorate quality of life.

Current management for CMP includes pharmacotherapies, surgical procedures, physiotherapy, multimodal pain management, exercise therapy, psychological interventions, and acupuncture. Pharmacotherapies including opioid medication (OM) are routinely used but are associated with many and serious adverse effects, such as risks of addiction, dependence, uncertain long-term benefit and death.

Chinese medicine (CM) including acupuncture has more than 3,000 years of history and it has been used to treat CMP. Clinical decision making is based on the diagnostic pattern guided by the CM unique theory and determined by evaluating the presenting pain and non-pain symptoms of CMP patients. For example, low back pain due to CM kidney deficiency pattern would also have non-pain symptoms such as lassitude, feverish sensation in the palms/soles or cold limbs. Chinese medicine incorporates the accompanying symptoms and/or comorbidities to understand and manage CMP which reflects the holistic approach. However, such an approach has not been evaluated by clinical trials to determine the value of pattern identification in the CM management for CMP, particularly for users of OM for CMP control.

In order to establish a basis for further research into CM for CMP, there is a need to identify the CM patterns of CMP and assess their differences with clinical outcomes measured by validated tools.

The Objectives of this thesis were to:

1) identify the comorbidities and symptomatologies of CMP through a systematic review;

2) develop and validate a Chinese medicine Pain Questionnaire (CMPQ) for pattern

identification in CMP patients who are OM users;

3) differentiate the CM patterns of CMP who use OM for pain control using cluster analysis; and determine the cluster differences in demography, pain intensity, OM consumption, depression, quality of life, and disability; and

4) determine the differences between CM patterns and clinical outcomes of electro acupuncture (EA) based on the change in CMPQ symptoms, pain intensity, OM consumption, depression, and quality of life.

To address Objective one, a systematic review was completed. Major English databases were searched and 72 studies were included with 61 of them being categorised into three main groups: chronic spinal pain, arthritis, and fibromyalgia. The findings showed the association between CMP and comorbidities and accompanying pain or non-pain symptoms for chronic spinal pain and arthritis but not for fibromyalgia. Chronic spinal pain (20 studies) was associated with (odds ratio 1.33-7.9) arthritis, headache/migraine, depression, and panic attacks/disorder, hypertension, heart diseases, general anxiety disorder, mood disorder, alcohol use disorder, and digestive ulcer. Arthritis (37 studies) was associated with (odds ratio 1.48 – 8.7) chronic spinal pain, depression, panic disorder, post traumatic stress disorder, heart disease/attack, asthma, headache, any chronic pain, and any physical disease. The current systematic review revealed that 15 fibromyalgia studies did not report odds ratio data on the same comorbidities. The association between comorbidities and fibromyalgia remains unconfirmed. Fibromyalgia patients were found to suffer from fatigue (95%), depression/depressiveness (90.9%), anxiety (77.7%), irritable bowel syndrome (62%), and irritable bladder (58%).

To address Objective two, CM literature was reviewed and a draft CMPQ was developed. Chinese medicine pain questionnaire contained 187 questions in the following six domains: pain regions, pain quality, pain rhythm, pain aggravators, pain alleviators, and other accompanying symptoms. These questions were reviewed by a group of CM researchers for face and content validities. The draft CMPQ was subsequently tested amongst CMP who used OM for pain control. This procedure was incorporated into a clinical trial titled "Electroacupuncture on opioid consumption by patients with chronic musculoskeletal pain: a randomised controlled trial" [1]. The CMPQ was completed by these subjects four times throughout the trial at pre-baseline (week one), baseline (just before randomisation and

commencement of the three assigned treatments - real EA, sham EA and no-EA) (week five), mid treatment (week 10), and at the end of treatment (week 14). In total 108 participants were recruited. The participants mostly had seven or more pain sites (55.6%). Many of them had pain in the lower back (78.20%), knee (48.50%), hip (47.50%), neck (44.60%), shoulder (41.60%), middle back (41.60%), and thigh (40.60%). Most of them had sharp pain (58.4%), pain at a fixed location (42.6%), pain all the time (63.4%), and worse pain when first getting up (42.6%). They were often accompanied with: feeling tired easily (69.20%), insomnia (59.40%), limited movement (56.40%), poor concentration (55.40%), poor memory (48.50%), feeling depressed (47.50%), irritable (45.50%), constipation (44.50%), and low libido (41.60%). Chinese medicine pain questionnaire demonstrated good face validity, content validity, test-retest reliability (Correlation coefficient=0.846 for overall questionnaire), and internal consistency (Cronbach's α=0.931).

To address Objective three, the CMPQ data gathered throughout the trial was analysed firstly using principal components analysis to extract 36 factors from the five CMPQ domains (except for pain region). Then the extracted factors were clustered using K-means cluster analysis into six clusters. Cluster four (n=48) and cluster five (n=41) had the largest number of participants and they were diagnosed as CM "heat pattern" (cluster four), and "cold with deficiency pattern" (cluster five) respectively by the CM cluster analysis group experts. Of the remaining clusters, only clusters two and six had more than one participant. Multivariate analysis of variance on their demographic data showed cluster four had the shortest mean pain history (10.14 years) whereas cluster six had the longest pain history (24.71 years). When the CM "heat pattern" (cluster four) was compared with the CM "cold with deficiency" pattern (cluster five), the CM "heat pattern" was associated with the better quality of life and mild depression whereas the CM "cold with deficiency pattern" was associated with worse quality of life and moderate depression.

To address Objective four, baseline and end of treatment weeks CMPQ data were used. The comparison was within individual changes rather than between group changes. It was shown that real EA was the only group without deterioration, sham EA and pain and medication management (PMM) alone both had two symptom deteriorations. Sham EA was the group with most symptom improvements (nine symptoms) followed by PMM alone (four symptoms) and real EA (two symptoms).

To identify which pattern reported better response to real EA, cluster four “heat pattern” and cluster five “cold with deficiency pattern” were used as they had more participants. This comparison was within individual changes rather than group changes. The heat pattern subgroup reported improvement in one more symptom on CMPQ in response to real EA than the cold with deficiency pattern subgroup.

Baseline and end of treatment weeks data of pain intensity, OM consumption, depression, and quality of life of the three treatment groups and the two CM patterns (clusters four and five) were compared. These were group mean comparisons and not changes within individuals. There were no differences between the three treatment groups, neither was there any difference in how the two CM patterns responded to the three treatments.

In conclusion, this project employed an evidence-based medicine approach to identify symptom presentation in CMP patients who use OM for pain control, developed and validated the CMPQ for clinical sub grouping guided by CM theory and diagnosis. Furthermore, a preliminary analysis on potential relationship between CM patterns and clinical outcome was conducted as part of a multicentre RCT on EA for CMP who used OM. The finding of distinct heat and cold with deficiency patterns in CMP indicates the importance of incorporating some form of heat therapy, such as moxibustion, into future acupuncture studies for chronic pain.

The main limitation of this thesis is the small sample size during the evaluation of treatment effect of the three treatments and when the real EA group was further sub grouped into the two CM patterns. Further validation of the CMPQ in larger and different study populations is needed to determine the clinical benefit of CM patterns in clinical practice of EA for CMP. In addition, the use of likert scales instead of a dichotomous format to capture subtle changes after intervention is recommended. It is anticipated that a validated CMPQ may enhance the clinical benefit of multidisciplinary approach for the management of CMP.

1. Introduction

1.1 Problems associated with CMP and its management

Chronic musculoskeletal pain, a chronic muscle and bone disorder, is defined as pain that lasts beyond three months [2]. Chronic musculoskeletal pain affects a great portion of people. Both Australian data and the Netherlands national survey results found one in five people had CMP [3,4]. Chronic musculoskeletal pain affects patient's quality of life (QoL) [5], working status [6], and is costly to manage [7]. In Australia, the absenteeism cost due to chronic pain is estimated to be 1.4 billion/year, and the cost rises to 5.1 billion/year if reduced work performance is added [8]. Chronic pain causes approximately one in five patients to lose their job [9], and is an international health priority in the industrialised nations [10]. Chronic musculoskeletal pain has no cure [11], is considered to be a disease of its own in modern pain medicine [12], and should be understood and treated differently from acute pain [13].

Apart from pain, CMP is often accompanied with other diseases or health conditions (i.e. comorbidities) [14]. A systematic review (SR) [15] showed that the prevalence of comorbid hypertension in arthritis (50.8%) was almost three times as much as in asthma (18%). Comorbidities associated with CMP increase the disease burden to individuals and the society. A Swedish study in 2012 found that the cost per person for managing osteoarthritis (OA) plus depression (53619 Swedish Krona (SEK) (equivalent to 7,803 Australian dollars (AUD)) was 1.52 times more than managing osteoarthritis alone (35046 SEK (equivalent to 5100 AUD)); and the cost for managing back pain plus depression (46909 SEK (equivalent to 6,827 AUD) was almost twice as much as managing back pain alone (26152 SEK (equivalent to 3,806 AUD) in the year of 2006 [16]. Such impacts create wealth depletion in later life to the individual [17], not to mention the impact of comorbidity on CMP patients' social functioning [18]. All of these impede CMP patient's ability to fulfil their role within their work and relationships with relatives, reduce their QoL [19], and negatively impact their financial status. Comorbid pain at multiple sites reduces patient's physical functioning [20]. Unless these multiple sites of pain are addressed well together, the disability remains [20]. Comorbidities should be addressed concurrently when managing CMP for a better health results. There is a need to identify the comorbidity and the accompanying symptoms of CMP and their association with CMP in order to better understand CMP.

Currently the management of CMP focuses on pain relief and pain coping through the use

ofpharmacotherapies and non-pharmacotherapies. Pharmacotherapies include non-steroidal anti-inflammatory drugs (NSAIDs), steroids, and opioids [21]. Strong opioids is the World Health Organization's (WHO's) last stage of pharmacotherapy for pain management [22]. The Australia data shows the prescription of oxycodone, in mg/capita, has increased more than 90 times from 1980 to 2014 [23] and the number of prescriptions has increased 152% from 35.3/1000 adult population in 2002-2003 to 89.2/1000 adult population in 2007-2008 in the population [24]. This indicates an enormous increase of demand and almost one in ten adult Australians consumes oxycodone.

These pharmacotherapies come with severe side effects including opioid misuse which can lead to death of the patient [25]. Studies have shown pharmacotherapy may induce comorbidities. NSAIDs can cause hypertension [26,27] and congestive heart failure [27], and steroids can cause diabetes mellitus [28]. Old age and female populations are prone to multimorbidity [29,30]. This may be due to the older person having poorer functioning of liver and kidney which can cause the drugs to stay in the body for a longer period and increase the risk of side effects [31]. These figures show that CMP comes with multiple comorbidities and raise issues about the effectiveness, management adequacy, safety, and suitability of current pharmacotherapy, especially opioids, for addressing CMP.

1.2 Acupuncture and its role in pain management

One of the non-pharmacotherapies for CMP is acupuncture [21]. Acupuncture is recommended for joint pain/stiffness, post-operative pain, and muscle spasm by the United State of America (USA) Agency for Healthcare Research and Quality (AHRQ) guideline [32] and has shown consistent improvements for insomnia [33], and chronic low back pain (LBP) with depression [34]. Currently there are conflicting recommendations for CMP from various SRs. Some support the use of acupuncture for CMP [35] whereas some remain inconclusive [36,37]. One problem with acupuncture clinical trials is the acupuncture protocol. Traditionally acupuncture treatment is based on the CM patterns which are the basis for formulating the treatment principles [38]. Chinese medicine patterns are subgroups within conditions/diseases. They are diagnosed based on the presenting symptoms and signs of patients [38]. For instance, in chronic LBP, if the chronic LBP is accompanied with heaviness in the body/head/lumbar area, then such chronic LBP is due to the CM pattern of "dampness retention"; if chronic LBP is sharp in nature, at a fixed location, worse at night and better during the day, then such chronic LBP is due to CM pattern of "blood stasis". It is clear that chronic LBP in CM is not just about pain in the low back area.

It encompasses non-pain signs and symptoms that are often associated with LBP. The treatments for different CM patterns differ and different CM patterns may respond to the same acupuncture protocol differently. Viewing all accompanying symptoms together with CMP to identify comorbidities and co-occurring symptoms has been proposed by Hartvigsen et al. as the first line of CMP diagnosis [39]. This is in line with CM's holistic view of health and the principles of CM diagnosis.

Research data on CM patterns for CMP are, however, lacking. The current textbook information has been generated by experts based on their own experience, but is not based on research and whether such information reflects reality is unknown. In addition, CMP is a western medicine concept. Its closest CM counterpart is "Bi syndrome", which refers to pain of muscles and joints and is similar to the western medicine disease category 'arthritis'. While some instances of CMP are due to arthritis, others are not. There is a need to identify the CM patterns of CMP using evidence-based approaches. In order to achieve this, valid CM pattern identifications are needed and an objective and reliable tool reflecting CM theory is required. Such a tool needs to be scientifically sound and scientifically developed.

In order to address this knowledge gap, this project, which was embedded in an EA trial, utilised evidence based approaches to develop and validate the CMPQ, using the convenience sample of the clinical trial participants to identify the CM patterns of people with CMP who use OM for pain control.

1.3 Aims and objectives

The aims of this study were to develop and validate CMPQ through an evidence based approach for people with CMP who use OM for pain control; to explore the CM patterns present; and to evaluate the effects of a standard EA protocol on different CM patterns.

Specifically the objectives were to:

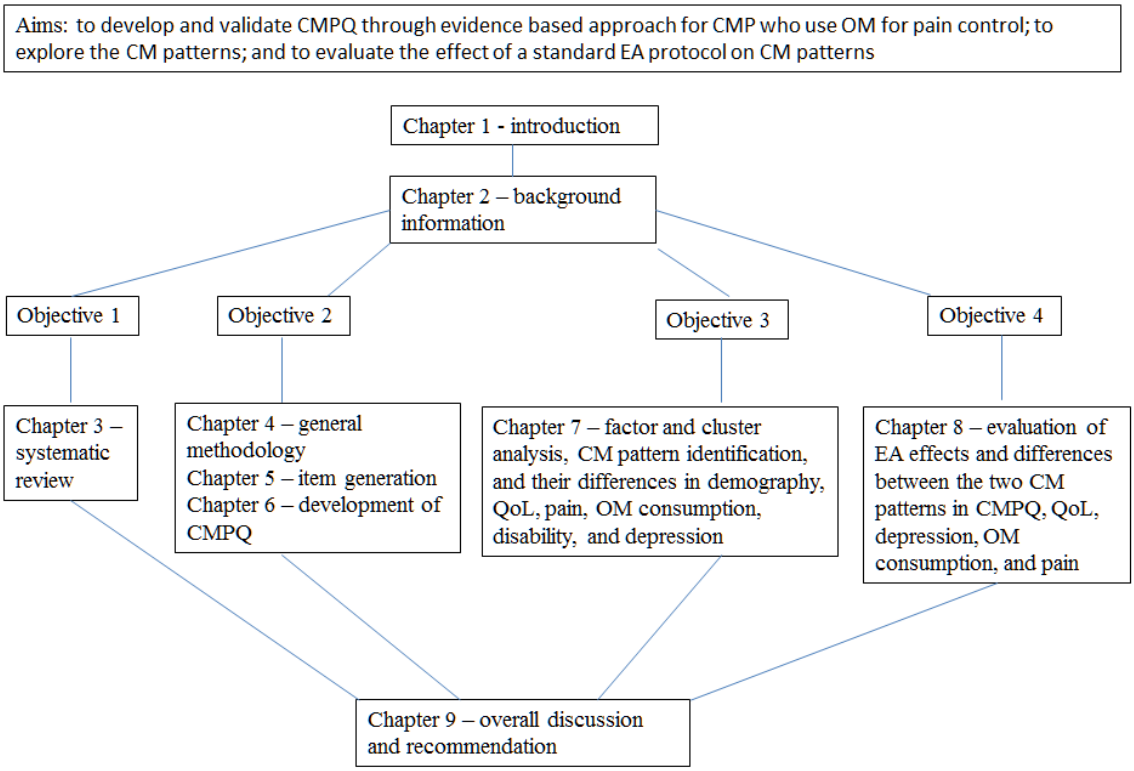
1) identify the comorbidities and symptomatologies of CMP through a SR (Chapter three);

2) develop and validate a CMPQ for pattern identification in CMP patients who are OM users (Chapters five and six);

3) differentiate the CM patterns of CMP who use OM for pain control using cluster analysis; and determine the cluster differences in demography, pain intensity, OM consumption, depression, QoL, and disability (Chapter seven);

4) determine the differences between CM patterns and clinical outcomes of EA treatment based on the change in CMPQ symptoms, pain intensity, OM consumption, depression, and QoL (Chapter eight).

These aims, objectives, and the structure of the thesis are outlined in Figure 1.1.



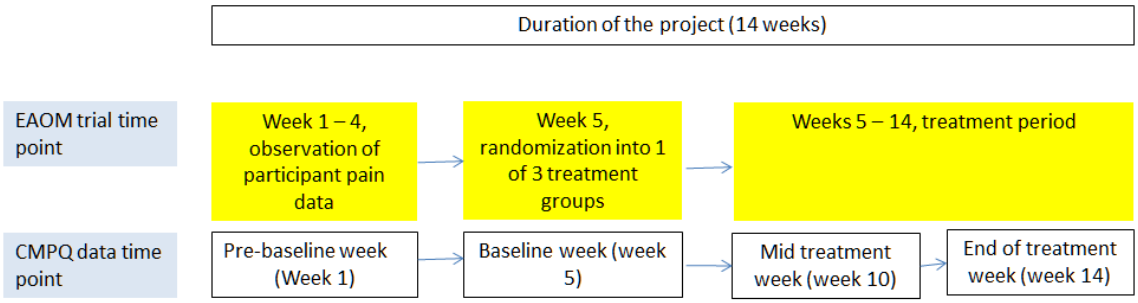
CM: Chinese medicine
CMPQ: Chinese medicine pain questionnaire
EA: Electro acupuncture
OM: Opioid medication
QoL: Quality of life
Figure 1.1 The structure of the thesis

1.4 Organization of the thesis

This project was embedded in a clinical trial titled "Electroacupuncture on opioid consumption by patients with chronic musculoskeletal pain: a randomised controlled trial" (EAOM trial) 1.

To develop and validate CMPQ, data collected from CMP patients who took part in the clinical trial were used. The design and methods of the EAOM trial is described from Chapter 4.2 Initial development of CMPQ (p. 141) to Chapter 4.2.3 Procedure of the EAOM trial (p. 142) and Chapter 8.2.1 Participants (p. 260).

A comparison of the time points of various data collections and interventions between the trial and this current project is illustrated in Figure 1.2.



1) pre-baseline week refers to data collected on week one
2) baseline week refers to data collected on week five, prior to randomisation and commencement of the three assigned treatments (real EA, sham EA, and PMM alone), and baseline weeks refers to the average data from week one to four.
3) mid treatment week refers to data collected in week 10 of the trial (week ten); and
4) end of treatment week refers to data collected in week 14, at the end of the trial, and end of treatment weeks refers to the average of data from week 11 to week 14.
Figure 1.2 CMPQ data time point in relation to EAOM trial time point

Table 1.1 Time points and their data usage in CMPQ validation, CM pattern identification, and evaluation of treatment effects

CMPQ validation and other applications	**Pre-baseline weeks**	**Baseline week**	**Mid treatment week**	**End of treatment week**
Internal consistency	x			
Reproducibility (test-retest reliability)	x	x		
Responsiveness		x	x	x
CM pattern identification		x		
Evaluation of treatment effect.		x		x

The CMPQ properties, CM pattern identification, and treatment effects with regard to CMPQ data usage are illustrated in Figure 1.2 and Table 1.1. Internal consistency was evaluated using

the CMPQ data collected at pre-baseline week. Reproducibility was evaluated using the CMPQ data collected at pre-baseline and baseline weeks (Table 1.1). Chinese medicine patterns were diagnosed based on factor and cluster analysis of symptoms using baseline week CMPQ data (Table 1.1). Responsiveness was evaluated using CMPQ data of baseline, mid treatment, and end of treatment weeks (Table 1.1).

The relationships of the two largest CM patterns and the commonly used outcome measures for CMP, including pain and medication data, Medical Outcome Short Form Health Survey 36 items (SF36) for QoL, and Beck Depression Inventory (BDI) for depression, were also explored. The changes in the three treatment groups between baseline and end of treatment weeks were also evaluated for the two largest CM patterns with CMPQ, and the other commonly used outcome measures (Table 1.1).

The thesis consists of nine chapters. These are briefly described below:

Chapter one introduces the background information and the outline of the project.

Chapter two outlines the epidemiology, impact, current management, comorbidities of CMP as well as a brief introduction to CM, including how CM diagnoses CMP, the efficacy of acupuncture for pain management, and current issues with acupuncture in pain management. This chapter identifies the knowledge gaps in current pain management and the CM pattern diagnosis of CMP.

Chapter three presents a SR on the comorbidities and accompanying symptoms of CMP following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [40]. Data from 72 cohort, case-control, and cross sectional studies were collected and analysed. Risk of bias was assessed using Newcastle Ottawa Scale (NOS) [41]. The methods of comorbidity assessment, odds ratio (OR) and percentage data of comorbidities and accompanying symptoms of three major types of CMP are reported. The results are grouped based on International Classification of Disease into twelve categories [42]. This chapter identifies the multiple comorbidities of CMP and their degree of association.

Chapter four describes the methodology used for the development and validation of CMPQ. Fundamental information on the reliability and validity of the questionnaire are presented here

as well as the composition of the expert groups for assessing the validities of CMPQ and CM pattern diagnosis of the clusters identified in chapter seven. The EAOM trial methods are also described here.

Chapter five describes the item generation of the CMPQ. Information on the construction and domains of CMPQ and the CM interpretation of the generated items are described.

Chapter six presents the validation result of CMPQ, specifically the content and face validities, reproducibility, internal consistency, and responsiveness data. The frequency analysis of signs and symptoms collected with CMPQ at pre-baseline week are also presented. Refer to Table 1.1 for the usage of CMPQ data time points and CMPQ validities.

Chapter seven presents the CM pattern identification using the factor and cluster analyses of baseline week CMPQ data. The two CM patterns of “heat”, and “cold with deficiency” that were identified are discussed.

Chapter eight examines the treatment effect on the CM patterns. It presents the effect of EA (both real and sham) and PMM alone on CMP patients who took OM for pain control on changes in pain and non-pain symptoms. The treatment effects in the two largest clusters (or CM patterns) were compared. Both baseline and end of treatment week CMPQ data were used for treatment effect evaluation. Moreover, the association between the two largest CM patterns and the other outcome measures were explored.

CM “heat pattern” was associated with better QoL and depression whereas CM “cold with deficiency pattern” was associated with worse QoL and depression. The two CM patterns did differ in their pain and OM consumption.

Chapter nine is the general discussion of the overall findings of the project. Limitations and recommendations for both clinical practice and future researches are discussed

2. Literature review

2.1 Chronic pain

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [43]. Chronic pain is defined as having such an unpleasant experience persistently for three months or more [44]. Musculoskeletal is defined as pertaining to muscles and skeleton [45(p1135)]. Chronic musculoskeletal pain includes pain in the cervical thoracic, lumbar, sacral, and coccygeal regions of the spine as well as pain in the shoulder, upper arm, elbow, forearm, wrist, hand, finger, hip, thigh, knee, leg, foot, and toes. Diseases and conditions leading to CMP include OA, rheumatoid arthritis (RA), rheumatic arthritis, fibromyalgia/chronic widespread pain, frozen shoulder, and tennis elbow. Chronic musculoskeletal pain also includes pain due to vertebral disc protrusion but does not include carpal tunnel syndrome according to International Classification of Disease by WHO [46].

2.2 Prevalence of CMP

In Australia, one in five people are affected by CMP [3] and 55.8% of women and more than 40.5% of men over the age of 65 years are affected by arthritis or rheumatism [47]. Different countries have reported different prevalences for CMP. A recent study in Norway found that the prevalence of musculoskeletal pain ranged from 9.8% to 34.7% amongst adults (n=3179) [48]. A Swedish study found the most common musculoskeletal pain areas were back (22.7%) and shoulder (21.0%) among people between 20-64 years old [49]. A cross sectional postal survey found chronic widespread muscle pain and chronic localized muscle pain affected 22% and 25% of Norwegian women respectively (n=2264) [50] whereas a review found generalized musculoskeletal pain was present in 38-57% of population [51]. An international collaborative survey in Colombia, Mexico, USA, Belgium, France, Germany, Italy, Netherlands, Spain, Ukraine, Israel, Lebanon, Nigeria, South Africa, Japan, China (Beijing and Shanghai), and New Zealand found 16.5% to 20% of adults in the general public suffered from arthritis/joint pain and chronic back pain respectively. In general, over one in four people suffered from CMP.

Musculoskeletal pain affected all age groups. A Brazilian epidemiological study on 3,269 children aged between 10 – 17 years old found that more than 15% of children had neck, knee, wrist or hand, or upper back pain [52]. The 451 working children amongst them had pain in the neck (42.9%), shoulder (19.0%), wrists or hands (42.9%), upper back (23.8%), and thigh

(19.0%) [52]. Hungarian data showed 25.8% of young Hungarian women aged 15-24 years old (n=3,615) had CMP [53]. According to an epidemiologyical study in the Uppland region of Sweden on adults aged 20-64 years (n=4,506) the prevalence of CMP increased with age [49] whereas another Swedish study in a rural population found the prevalence of chronic pain increased up to 50-59 years for both genders and then decreased [54]. A USA prospective cohort study that included 1,002 community dwelling women older than 65 years identified that up to one in four suffered from chronic widespread pain [55].

2.3 Impact of CMP

Musculoskeletal pain impacts a person in many different ways. The following sections list its impact on QoL, working status, and cost of pain.

2.3.1 Impact on QoL

A Swdish study, published in 2008, investigated the association between health factors and health related QoL with an eight year follow up amongst participants with and without CMP, with subjects' age ranging from 20 to 74 years [56]. The study found CMP patients scored significantly lower (ranged from 50s to just above 80) than participants without CMP (ranged from low 70s to above 90) in all of SF36 domains at both the baseline and the eighth year follow up ($p<0.001$). This study only provided graphical comparisons without any mean and standard deviation.

An Irish study (n=498), published in 2008, reported CMP patients had lower health appraisals, especially among the elderly aged over 60 years, when compared with the average of the whole sample (average age not supplied in the manuscript) [5]. As people got older, fewer and fewer patients believed they were in a good health [5]. Amongst the patients, 49% were limited in some work activities and 44% accomplished less than they had expected in the previous four weeks [5]. As assessed with Medical Outcome Short Form Health Survey 12-Item (SF12), 67% of the patients had poorer QoL in comparison with the average health appraisal (mean data not provided) [5].

A Hong Kong study, published in 2009, investigated the impact of musculoskeletal pain in elderly Chinese [57]. It included 4,000 participants with equal numbers of both genders [57]. This study found CMP patients had reduced grip force, slower walking speed, reduced step length,

lower level of physical activity, poorer perception of self health, depressive symptoms, and lower QoL score (assessed with SF12). Their daily activities were significantly impacted [57]. Women were affected similarly to men except that women had increased fracture incidence [57].

2.3.2 Working status

An Australian study examined the impact of chronic pain on working status [58], and found that over six months, workers with chronic pain had 83.8 working days with pain and a 14.2% reduction in work effectiveness. They also lost 4.5 working days due to pain. When the working days with pain and reduced work effectiveness were added to the 4.5 lost working days, in total the workers lost 16.4 working days equivalence over six months.

One Finnish study, published in 2009, looked at the effect of upper extremity disorders on working status [6]. It included 168 patients with upper extremity disorders [6]. Amongst the patients, 64% were nurses and other health care workers, 25% were secretaries and other clerical workers, 8% were warehouse workers, and 87% of them were females [6]. Thirty seven percent of the patients had sickness absence in the last 12 months due to upper extremity disorders. Reduced productivity due to upper extremity disorder was reported by 56% of females and 59% of males [6]. The average loss in production was 34% in comparison to a normal work day [6].

A Norwegian study showed that LBP resulted in absence from work. The median duration of absence was 43 days with the 25^{th} and 75^{th} percentiles being 23 and 103 days. Only 35%, 70%, and 85% of these workers returned to work after one, three, and six months of sick leave. Of these workers, LBP with radiating pain resulted in longer duration of absence. The medians (25^{th}-75^{th} percentile) of days of absence for LBP with radiation versus LBP without radiation were 59 days (28-152 days) and 38 days (21-86 days) respectively [59].

2.3.3 Cost of pain

Reports published by Australian Institute of Health and Welfare in 2005 and 2010 showed the cost of health expenditure for musculoskeletal diseases to be 3.076 billion and 3.864 billion AUD for the period between 2000-2001 and 2004-2005 respectively [60]. This was a 26% increase in expenditure, higher than the average increase of 20%. Musculoskeletal disease group was also the third most expensive health expenditure amongst the list of the allocated health expenditure groups between 2004-2005 period [60].

Other costs for chronic pain in Australia in 2007 included loss of productivity due to absenteeism and presenteeism (3.8 billion AUD) and loss of potential tax revenue (including both personal income tax, and indirect personal tax) amounting to 3.69 billion AUD, and a dead weight loss of 1.06 billion AUD in additional taxation [8]. Dead weight loss here referred to the loss of tax when workers were unable to work due to sicknesses which led to reduced income and tax output.

Primary carers, who often were relatives and friends of chronic pain patients, were estimated to spend on average 26 hours per week to provide informal care for chronic pain patients which was estimated to cost 1.3 billion AUD in 2007 [8]. Other additional costs for chronic pain patients included aids, such as walking frames, walking sticks, crutches, wheelchairs, and modification around the home. The estimated cost for these was 331.7 million AUD in 2007.

Altogether the Australian data showed a total loss of 15.8 billion AUD per year for the non-medical costs, including the productivity loss, cost of carer, cost of aids and modifications, and cost of deadweight loss for chronic pain [8].

USA patients with chronic pain of spinal origin were estimated to spend 4,000 to 19,000 USD per year per patient on pharmacotherapy and physician visits [61]. The cost of an intrathecal implant was between 53,468 and 125,102 USD over five years [7]. Another review has quoted from Coyote et al. that in 1994 alone, the total cost of musculoskeletal disorders in Canada, including both direct and indirect costs, exceeded 25 billion Canadian dollars [62]. The direct costs here referred to expenses of hospital and other institutions, health professionals, pharmacotherapies, research, and other items not specified [63]. The indirect costs referred to productivity lost due to disability and premature mortality [63].

2.4 Current management of chronic pain

This section describes the common approaches of CMP management. They include pharmacotherapy, non-pharmacotherapy treatments, and multidisciplinary pain management (MPM).

2.4.1 Pharmacotherapies, its efficacy and safety

Pharmacotherapies for CMP include paracetamol (simple analgesic and antipyretic drug), oral

or topical NSAIDs, intra-articular corticosteroid injection, weak and strong opioids [21].

Paracetamol is simple analgesic and antipyretic drug [64]. Its mechanism on pain alleviation is uncertain but is thought of related to actions on cyclooxygenase three, the serotoninergic system, or on bradykinin-sensitive chemoreceptors [65].

Evidence for the effectiveness of paracetamol for arthritis is conflicting. One SR published in 2006 that included 15 randomised controlled trials, with a total of 5,986 participants, concluded that paracetamol was found to have a similar safety profile as placebo but worked less effectively than NSAIDs for knee or hip OA [66]. Another recent SR published in 2015 that included 13 studies with 5366 spinal pain (SP), OA of hip or knee participants concluded paracetamol was ineffective and only provided minimal short term benefit for OA [67]. A recent study had shown an association between paracetamol and increased incidence of hypertension [68]. Furthermore, paracetamol accounted for 11% of all pharmaceutical poisoning cases between 2009 and 2010 in Australia [69].

Non-steroidal anti-inflammatory drugs include aspirin, other salicylic acid derivatives, propionic acid derivatives, acetic acid derivatives, oxicam derivatives, fenamates, heteroaryl acetic acids, nabumetone, and celecoxib [70]. They act by inhibiting cyclooxygenase enzymes, which catalysed prostanoid biosynthesis, and lead to reduced prostaglandin production [70]. Prostaglandin has a function to regulate inflammation, pain, and fever [70].

One published expert consensus indicated the evidence for NSAIDs in treating hip OA is 1a, which means the highest level of evidence based on a meta-analysis of randomised controlled trials (RCTs) [71]. Topical NSAIDs for knee OA showed a good result, after four weeks of application, in comparison with placebo or vehicle [72]. The recommendation made for hip OA also indicated 1b for opioids, chondroitin sulphate, avocado soybean unsaponifiable, diacerhein, intra-articular steroid, and education; III for weight loss, hyaluronic acid, osteotomy, and total hip replacement [71].

Another SR investigated the efficacy of NSAIDs on LBP [73]. This SR included 65 trials with 11,237 participants and concluded NSAIDs were effective for short term relief of acute and chronic LBP without sciatica with a small effect size. The pain reduction ranged from -0.21 to -12.4 on a 100 mm visual analogue scale (VAS). The comparisons included placebo and

paracetamol.

Intra-articular corticosteroid injection: Steroids work by suppressing the inflammatory responses by affecting the concentration, distribution, and function of peripheral leukocytes, and suppressing the inflammatory cytokines and chemokines and other inflammatory mediators [28]. When glucocorticoids were applied, neutrophils increased while T and B cells, monocytes, eosinophils, and basophils decreased [28]. Glucocorticoids activated phospholipase A_2 which reduced prostaglandin, leukotriene, and platelet-activating factor synthesis and glucocorticoids reduced the expression of cyclooxygenase-two and subsequently reduced the available prostaglandins and reduced the inflammatory response [28].

Intra-articular corticosteroid administration has been shown to provide short-term symptomatic management for knee and hip OA [21]. Intra-articular corticosteroid was associated with complications and risks such as allergic reaction, swelling at site of injection, haematoma, fluid retention, hyperglycaemia (high blood sugar), and hypertension [21]. Even though it was effective for OA, its use was limited to three to four times per year with at least three months interval between each administration [21].

A SR assessed neuromodulators for RA [74] includeing nefopam, topical capsaicin and an oro-mucosal cannabis spray. The authors concluded there was weak evidence supporting these neuromodulators in reducing RA pain but the side effects of nefopam and oro-mucosal cannabis spray outweighed the benefit they produced.

2.4.1.1 Side effects of the above mentioned drugs

The above-mentioned three classes of drugs all have side effects (Table 2.1), which range from mild side effects, e.g. dizziness, nausea, insomnia, to severe side effects, e.g. hepatotoxicity with centrilobular necrosis, renal tubular necrosis, gastrointestinal ulceration/perforation. Care should be taken when prescribing these drugs.

Table 2.1 Side effects of pharmacotherapy

Pharmacotherapy	Side effects
Paracetamol	Increased hepatic enzyme, dizziness, excitement, disorientation, hepatotoxicity with centrilobular necrosis, renal tubular necrosis, haemolytic anaemia, methemoglobinemia
NSAIDs	Epigastric distress, abdominal pain, nausea, vomiting, dyspepsia to gastric bleeding, gastrointestinal ulceration, upper gastrointestinal perforation and bleeding, endoscopically detected gastroduodenal erosions, diarrhoea, prolonged bleeding time, bronchoconstriction, respiratory depression and a combination of uncompensated respiratory and metabolic acidosis, hyperthermia (large dose of salicylates), urticaria, angioedema, Reye syndrome, headache, tinnitus, dizziness, and haemolytic anaemia, peripheral oedema, hypertension, increased bleeding time, increased risk of myocardial infarction and ischaemic stroke
Intra-articular corticosteroid injection	Iatrogenic Cushing's syndrome, diabetes mellitus, hypothalamus/pituitary/adrenal suppression, proximal myopathy, tendon rupture, impaired growth (in children), vascular necrosis of bone, immunosuppression, peptic ulcer and haemorrhage, depression and psychosis, euphoria, insomnia, aggravation of schizophrenia and epilepsy, raised intracranial pressure with papilloedema, posterior subscapular lens cataract, glaucoma, corneal or scleral thinning, menstrual disorder, delayed tissue healing, thromboembolism, and paradoxical hypersensitivity reaction.

Information extracted from [26,28,70,75]
NSAID: Non-steroidal anti-inflammatory drug
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2.4.1.2 Opioid medications (OMs)

Opioid medication works by binding to the opioid receptors (μ, δ, and κ), which are also known as the G-protein -coupled receptors [76]. These receptors are located in the brain and pain transmitting and modulating regions in the spinal cord. When an opioid binds to the opioid receptors, it closes the Ca^{2+} channels and opens the K^{+} channels [76,77]. Such action inhibits the release of neurotransmitters, e.g. glutamate, acetylcholine, norepinephrine, serotonin, and substance P [76,77], and subsequently reduces pain sensation.

Opioid medication s can be differentiated based on their binding to particular opioid receptors and whether they are agonists e.g. morphine and hydromorphone or partial agonists e.g. codeine or hydrocodone, or are a mixture of agonist and antagonist e.g. nalbuphine and buprenorphine (Table 2.2).

Table 2.2 OM, agonist and antagonist to the receptor type

OM	Receptor type		
	μ	**δ**	**K**
Sufentanil		+	+
Morphine	+		+
Hydromorphone	+		
Oxymorphone	+		
Methadone	+		
Meperidine	+		
Fentanil	+		
Alfentanil	+		
Remifentanil	+		
Levorphenol	+		
Oxycodone	+		
Codeine	^		
Hydrocodone	^		
Pentazocine	^		+
Butorphenol	^		+
Nalbuphine	-		+
Buprenorphine	^	-	-

+: strong agonist
^ : partial agonist
-:antagonist
OM: Opioid medication
Empty cell means not this type of receptor.

Side effects of OM include: respiratory depression, tolerance, dependence, addiction, behavioural restlessness, tremulousness, increased intracranial pressure, postural hypotension accentuated by hypovolaemia, urinary retention, itching around nose, and urticaria. In addition, OM is associated with behaviours such as diversion of prescription opioids, opioid misuse in patients with chronic pain, activation of reward response (which may result in opioid dependence and opioid seeking behaviour, and difficulties in weaning patients off OMs), opioid-induced hyperalgesia, gastrointestinal side effects (such as constipation, delayed gastric emptying, nausea and vomiting), sleep disturbance, reduced sex hormones, and interference with the immune system [78]. A SR [79] reported the occurrence of long term OM side effects with apnea having the highest occurrance and opioid overdose and serious intestinal blockage having the least occurrance (Table 2.3).

Table 2.3 Side effects due to long term use of OM

Opioid side effects	Rate of occurrence.
Mild to severe central and/or obstructive apnea	As high as 75%
Cardiovascular events (myocardial infarction and heart failure)	77% increased risk
Comorbid depression	Up to 38%
Constipation	30-45%
Depression, anxiety, deactivation, apathy	30-40%
Hypogonadism, impotence, infertility, osteoporosis	25-75%
Opioid misuse	~25%
Nausea	25%
Breathing problems during sleep	25%
Disruption of sleep	25%
Dry mouth that may cause tooth decay	25%
Sedation	15%
Addiction, misuse, and diversion	5-30%
Falls causing hip and pelvis fracture	1-2% per year
Opioid overdose	<1% per year
Serious intestinal blockage	<1% per year
Hyperalgesia, myoclonus	Not known

Data extracted from Baldini et al. [79]

Opioid medications have a moderate effect on treating musculoskeletal pain and neuropathic pain with a pain reduction of at least 30% [80]. About 80% of the participants experienced at least one kind of side effect [80]. Opioid short term efficacy on CMP or neuropathic pain had been proven to be good with its long term efficacy being uncertain [21,80]. Long term (more than one year) effect of OM was not found in a SR [81], which reviewed literature from 2008 to 2014. Another clinical trial, with a 10 year follow-up period, on 160 chronic non-malignant pain patients found 60% of the patients still used OM at 10 year follow-up [82]. Withdrawal symptoms, including rhinorrhoea, tearing, yawning, chills, goosebumps, hyperventilation, hyperthermia, dilatation of pupil, muscle aches, vomiting, diarrhoea, anxiety, and hostility, would develop for patients who try to quit using OM [70]. It was found that patients on pre-existing OM consumption were 1.5 times more likely to drop out of a functional restoration programme, in comparison with patients who did not consume OM before the programme, where weaning off OM was a requirement [83].

2.4.2 Non-pharmacotherapy treatments of chronic pain

There are several non-pharmaceutical treatments available to treat chronic pain, including physiotherapy, multimodal physical therapy, self management education programmes, MPM, acupuncture, and surgery [21,71] and psychology [84].

2.4.2.1 Non-pharmacotherapy, invasive interventions and their efficacy

Non-pharmacotherapy, invasive interventions for CMP include acupuncture and surgery.

Surgery: The findings of studies of surgery for various musculoskeletal conditions/diseases are presented in Appendix 1. These SRs have recommended surgery for carpal tunnel syndrome [85] and symptomatic spondylolysis [86]. However, the best surgical procedure for sciatica due to disc herniation could not be confirmed [87], and there was a weak recommendation for surgery for lower extremity pain due to disc protrusion and no recommendation for surgery for axial pain due to disc protrusion [88]. Furthermore, there was no evidence to support the use of surgery for acromioclavicular dislocation [89] and rotator cuff disease [90]. Side effects/adverse reactions/complications of surgery (Appendix 2) include hardware complications such as screw breakage, screw pull out, wire breakage; and surgical procedure related complications such as wound infection, wound haematoma, delayed wound healing; or other complications such as stiffness at the operated site, pain, skin irritation, and reflex sympathetic dystrophy [85-90].

Acupuncture: Several SRs have assessed the effects of acupuncture on musculoskeletal disorders/diseases (Table 2.4). Acupuncture has shown effectiveness and efficacy on the severity of neck pain and related disabilities [91], severity of chronic LBP and function [92], and chronic pain [35]. Effectiveness refers to whether or not an intervention works in a routine setting and generally compares the intervention with another known intervention [93]. Efficacy refers to how beneficial is a specific intervention under an ideal situation [93] e.g. randomised sham/placebo controlled trial. Acupuncture was found to: 1) be inconclusive for lateral elbow pain [36]; 2) have a small but statistically significant effect for peripheral joint pain [94] when compared with sham control; 3) have no evidence for acute LBP [92] due to small sample size and low methodological quality; and 4) have little or no evidence for shoulder pain [37] when compared with placebo due to small number of trials and heterogeneity. The USA AHRQ guideline recommended acupuncture for joint pain/stiffness, soft tissue pain and inflammation, paraesthesia, post-operative pain, muscle spasm, and scar tissue pain [32].

For chronic pain, the SR by Vicker et al. [35] identified the effect sizes for acupuncture in comparison to sham control were a small (0.23 (95% C.I. 0.13, 0.33)) for back and neck pain, very small to small (0.16 (95% C.I. 0.07, 0.25)) for OA, and very small to small (0.15 (95% C.I. 0.07, 0.24)) for chronic headache; and the effect sizes for acupuncture in comparison to no acupuncture controls were medium (0.55 (95% C.I. 0.51, 0.58)) for back and neck pain,

medium (0.57 (95% C.I. 0.50, 0.64)) for OA and small to medium (0.42 (95% C.I. 0.37, 0.46)) for chronic headache. Effect size was interpreted according to Cohen [95(p25,26)].

MacPherson et al. conducted a survey in UK on the adverse events associated with acupuncture [96]. The author sent out questionnaires to patients receiving acupuncture treatment who agreed to participate the survey at the three months follow up after the acupuncture treatment (n=6,348). Their findings indicated the most frequent side effect/adverse event was severe tiredness or exhaustion (3.6%) (Table 2.5).

Table 2.4 Summary of different reviews on acupuncture for CMP

Study	Included studies	Included participants	Condition / disease	Intervention	Comparison group	Follow up	Conclusion
Gadau et al. 2014 [36]	19	1190	Lateral elbow pain	Acupuncture, electro acupuncture, moxibustion alone, or acupuncture plus moxibustion	Sham acupuncture, conventional therapy (including triamcinolone acetonide injection, pulsated ultrasound and/or massage, prednisolone / hydrocortisone injection, meloxicam tablets), and acupuncture	1 day to 1 year	Moderate quality studies suggest that acupuncture is more effective than sham acupuncture. The conclusion remains inconclusive due to included studies having at least one criterion rated as high risk of bias. The results were limited for other comparisons.
Manheimer et al. 2010 [94]	16	3498	Peripheral joint arthritis	Acupuncture or acupuncture plus other active treatment	Sham, wait list, other active treatment	8 and 26 weeks	Acupuncture shows statistically significant results when compared with sham or wait list. But such effect is small and can be due to expectation/placebo effects.
Furlan et al. 2005 [92]	35	2861	Low back pain	Acupuncture, dry needling, or acupuncture added to another active treatment	No treatment, placebo, sham therapy, other active treatment,	3, 6, and 12 months	No firm conclusion for acute LBP. For chronic LBP, acupuncture is not more effective than other interventions. Acupuncture is more effective than no treatment or sham treatment.
Trinh et al. 2016 [91]	27	5462	Neck pain	Acupuncture	Sham acupuncture, inactive treatment, wait list	3 months, 1 year,	Moderate evidence for acupuncture more effective than sham acupuncture

Study	Included studies	Included participants	Condition / disease	Intervention	Comparison group	Follow up	Conclusion
						more than 1 year	post treatment. There is moderate evidence that acupuncture is more effective than sham acupuncture, wait list or inactive treatment at short term follow up (≤ 3 months).
Green et al. 2005 [37]	9	525	Shoulder pain	Acupuncture, electro acupuncture, acupuncture plus mobilization/exercise	Placebo, steroid injection, ultrasound, nerve block, acupuncture alone, exercise, tragar	Only one trial had 20 weeks follow up	There is little evidence to support/not support acupuncture for shoulder pain.
Vicker et al. 2012 [35]	29	17922	Non-specific back/neck pain, shoulder pain, chronic headache or osteoarthritis	Acupuncture	Sham (placebo) acupuncture or no acupuncture control	From one month to 24 months	Acupuncture is effective for treating chronic pain conditions. And factors in addition to the specific effects of needling are important in the therapeutic effects of acupuncture

Table 2.5 Side effects of acupuncture treatment

Adverse events	Reported adverse event rate over 3 months
Adverse events associated with treatment response	
Severe tiredness or exhaustion	3.6%
Prolonged or unacceptable pain at site of needling	1.6%
Severe headache or migraine	1.2%
Unexpected, severe or prolonged worsening of symptoms	1.2%
Severe drowsiness (e.g. causing a potential hazard on the road)	0.8%
Severe dizziness or vertigo or loss of balance	0.8%
Severe sleeplessness	0.7%
Severe stiffness or numbness	0.7%
Skin infection affecting either local area where needled or extensive area over body	0.4%
Diarrhoea	0.4%
Severe agitation	0.4%
Severe nausea	0.4%
Severe nightmares	0.4%
Severe panic	0.3%
Vomiting	0.3%
Fainting	0.2%
Uncontrolled euphoria	0.2%
Severe disorientation	0.1%
Fit or seizure	0%
Adverse events associated with practitioner behaviour or equipment	
Needle left in patient	0.9%
Moxibustion burns to skin	0.4%
Electro-acupuncture problems (e.g. too strong a current resulting in pain)	0.2%
Being left alone/unattended in the treatment room for too long	0.2%
Needle breaking	<0.1%
Punctured internal organ such as needle penetrating lung	0%
Other events mentioned spontaneously by respondents	
Bruising at needling site	0.5%
Other events	0.4%
Aches and pains (not specified)	0.2%
Emotional/psychological reaction	0.1%
Tiredness/drowsiness	0.1%
Bleeding at needling site	0.1%

Information extracted from MacPherson et al. [96].

2.4.2.2 Non-pharmacotherapy, non-invasive interventions and their efficacy

Non-pharmacotherapy, non-invasive interventions include physiotherapy, multimodal physical therapy, self management education programmes [21], psychological therapy and MPM.

Physiotherapy: Physiotherapy includes treatments using various combinations of exercises, stretching, manipulation, ultrasound, superficial heat, short wave diathermy, laser therapy, Codman's exercises, wall-climbing exercises, continuous passive motion, manual therapy, dumb-bell gymnastics and massage [97]. One SR on the effect of exercise on knee OA showed both aerobic walking and quadriceps strengthening were helpful to reduce pain and disability associated with knee OA when compared with non-exercise controls which included education and lifestyle advice, support by telephone calls, no intervention, or sham exercise programme. The pooled effect size was between 0.32 to 0.52 for pain reduction and self reported disability [98]. Their pain and disability outcome measures were not described in this SR. One drawback of this SR was the authors did not separate the groupings based on the control groups [98].

An SR on manipulation or mobilisation for neck pain [99] included 27 trials which included 1,522 participants who either had acute/subacute/chronic neck pain. The finding stated that cervical manipulation and mobilisation showed similar results. Both methods showed immediate or short term change and no long term data was available. Thoracic manipulation also showed an effect on the neck pain and function, but due to the low quality of the included trials, the author could only conclude that thoracic manipulation may improve neck pain and function.

One SR on physiotherapy intervention for ankylosing spondylosis included 11 trials with 763 participants [100]. The authors found combined inpatient spa-exercise therapy followed by group physiotherapy was better than group physiotherapy only. Supervised physiotherapy was better than home exercise. Home exercise of supervised exercise was better than no treatment.

Multimodal physical therapy: Based on one meta-analysis, the evidence showed multimodal physiotherapy, which involves quadriceps muscle retraining, patellofemoral joint mobilization, and patellar taping, and daily home exercises, provided short term (three months) relief for anterior knee pain when compared with placebo interventions (including flat insert orthoses, or sham physiotherapy which includes placebo taping, sham ultrasound, and the light application of a non-therapeutic gel) [101].

Self-management education programme: A self-management education programme has been shown to help arthritis pain. A RCT involving self-management of arthritis and an education booklet group (n=406) was compared with education booklet group alone (n=406) [102]. The self-management group was found to experience reduced anxiety, as assessed with

Hospital Anxiety and Depression Scale, without impact on pain, physical functioning and rate of general practitioner visits.

A SR examined patient education for LBP [103]. The review included 24 studies, of which three studies were on chronic LBP. Of the chronic back pain studies, patient education was less effective than non-educational interventions (e.g. physiotherapy, spinal stabilization, yoga, exercise, modified Swedish back school programme) for long-term back pain specific functional status. But there was generally no difference between patient education and non-educational intervention for pain, short term back pain specific function, general functional status, global improvement, and return to work. The short term was defined as between randomisation and six months whereas long term was defined as six months or more in this SR. The author could not confirm the effectiveness of patient education for chronic LBP.

Psychological therapy:

Cognitive behavioural therapy (CBT): A SR on CBT for any kind of chronic pain apart from headache and pain due to malignancy included 23 studies with 1,199 participants [104]. The author defined follow up period as between six months to 12 months and if there were multiple follow ups in this period, the later one was used. The summary is listed in Table 2.6.

The review found that CBT compared with treatment as usual (treatment not summarised in the review), showed statistically significant pain reduction after treatment (effect size -0.19 95% confidence interval (CI) -0.32 – -0.05) and a small improvement (effect size -0.16 95% CI -0.31 - -0.01) at follow up for mood. Cognitive behavioural therapy's effect on disability and mood was not statistically significant after treatment and at follow up for pain reduction and disability.

When CBT was compared with active control (treatment not summarised in the review), disability improved after treatment ($Z=2.20$, $p<0.05$. The effect size was -0.16 with 95% CI -0.31 - -0.02). The follow up data showed CBT had a significant overall effect on pain (12 studies with 935 participants, $Z=2.27$, $p<0.05$. The effect size was -0.15 with 95% CI -0.28 - -0.02), on disability (11 studies with 876 participants, $Z=2.71$, $p<0.05$. The effect size was -0.21 with 95% CI -0.36 - -0.06), and on mood (12 studies with 934 participants, $Z=2.44$, $p<0.05$. The

effect size was -0.16 with 95% CI -0.29 - -0.03) when compared with active control (treatment not summarised in the review). The result on pain and mood were not significant after treatment between CBT and active control.

Table 2.6 Summary of SRs of CBT for chronic pain

Number of studies	Number of participants	Types of comparison	Timing of assessment	Types of assessment	Effect size	95% CI
23	1199	Treatment as usual (treatment not summarised in the review)	After treatment	Pain	-0.19	-0.32 – -0.05
9	693		Follow up		NS	
18	972		After treatment	Disability	NS	
8	496		Follow up			
16	839		After treatment	mood	NS	
9	684		Follow up		-0.16	-0.31 - -0.01
14	861	Active control (treatment not summarised in the review)	After treatment	pain	NS	
12	935		Follow up		-0.15	-0.28 - -0.02
12	728		After treatment	disability	-0.16	-0.31 - -0.02
11	876		Follow up		-0.21	-0.36 - -0.06
15	890		After treatment	Mood	NS	
12	934		Follow up		-0.16	-0.29 - -0.03

CI: Confidence interval
NS: Not significant
Information extracted from Eccleston et al. [104].

Behavioural therapy (BT): The previously mentioned SR also assessed the effect of BT on chronic pain apart from headache and pain due to malignancy [104]. The results are summarised in Table 2.7. The effect of BT was only better when compared with treatment as usual (treatment not summarised in the review) for pain after treatment (nine studies with 430 participants, $Z=3.03$, $P<0.05$. The effect size was -0.55 with 95% CI -0.90 - -0.19) but not at follow up (six to twelve months after treatment). For disability and mood, both after treatment and at follow up showed no difference. There was no difference between BT and active control (treatment not summarised in the review) for pain, disability, and mood both after treatment and at follow up.

Table 2.7 Summary of SR of BT for chronic pain

Number of studies	Number of participants	Types of comparison	Timing of assessment	Types of assessment	Effect size	95% CI
1	39	Active control (treatment not summarised in the review)	After treatment	Pain	NS	
1	39		Follow up			
2	110		After treatment	disability	NS	
2	110		Follow up			
2	110		After treatment	mood	NS	
2	110		Follow up			
9	430	Treatment as usual (treatment not summarised in the review)	After treatment	Pain	0.55	-0.90 - -0.19
3	232		Follow up		NS	
7	374		After treatment	disability	NS	
3	230		Follow up			
6	357		After treatment	mood	NS	
3	230		Follow up			

CI: Confidence interval
NS: not significant
Information extracted from Eccleston et al. [104].

Multidisciplinary pain management

Multidisciplinary pain management refers to the utilisation of multiple therapies to manage CMP [105]. Such therapies include primary care physician, psychiatrist, physiotherapist, occupational therapist, and psychologist and/or trained counsellor. In addition, the MPM team may also include a recreational therapist, biofeedback specialist, social worker, case manager, an ergonomics therapist, pharmacist, addictionologist, dietician/nutritionist, and may include a priest [105]. Some of the therapies have been described in this section. The following section focuses on MPM as a team rather than discussing the individual therapies.

Multidisciplinary pain management has the following goals [105]:

1) To empower patients and family through educating them and enabling them to participate in treatment decisions;

2) Improve patient's function and activities of daily living through providing them knowledge

and training;

3) Reduce patients' dependence on drugs by reducing patients' consumption of OM, benzodiazepine, antidepressant and antiseizure drugs. Benzodiazepine is a sedative which produces drowsiness and enhances the onset of sleep [106];

4) Reduce patients' dependence on health care systems by teaching the patient self management skills;

5) Reduce patients' reliance on family members and other people by encouraging family members and other people to show empathy rather than sympathy towards patients;

6) Decrease patients' pain behaviours by informing patients to have wellness behaviour;

7) Enabling patients to return to work if possible and maybe a changing in job to enable the patients to commence work; and

8) Improve patients' QoL.

A non-randomized clinical study that investigated the effect of MPM and usual care (UC), which comprised of non-multidisciplinary physiotherapy and non-surgical treatments, and showed improvement in QoL with significant differences between MPM and UC at six months follow-up in role limitations, physical (MPM:UC=19±39:7±31, $p<0.01$); bodily pain (MPM:UC=18±25:7±23, $p<0.01$); social functioning (MPM:UC=15±21:5±24, $p<0.05$); role limitations, emotional (MPM:UC=16:50:3±42, $p<0.05$.); emotional well-being domains (MPM:UC=8±17:3±16, $p<0.05$) and the physical (MPM:UC=4.9±8.0:2.6±6.8, $p<0.05$) and mental (MPM:UC=4.4±11:1.8±10, $p=0.1$) components summary in SF36, reduced days off work (average reduced 16 days off work in the MPM group in comparison to two additional days off work in the UC group), and 54% of patients in the MPM group and 24% of UC patients felt the restriction that LBP had in their life was better [107].

A SR on MPM that included 11 studies, looked at the long term effectiveness of MPM at six months to 12 months, on chronic pain [108]. The review found the treatment effect on pain

perception was still maintained at 12 months follow up, but the effect on self-efficacy decreased at 12 months follow up. The treatments mainly included education, pacing, relaxation, and goal setting. Three studies had the pain management in the inpatient setting whereas the other seven had it in the outpatient setting. One study did not describe the setting of the pain management. Other SR pointed out that MPM improved pain, mood and interference, as well as return to work status, and use of healthcare system [109]. Overall, MPM may fail but does not carry the severe complication of surgery [105].

In summary, physiotherapy was shown to benefit pain and disability of knee OA [98], pain and function of neck pain [99], and physiotherapy was better than no treatment for ankylosing spondylosis [100]; multimodal physical therapy improved anterior knee pain with short term relief [101]; and CBT and BT had weak effects in reducing chronic pain and minimal effects for disability associated with chronic pain. Cognitive behaviour therapy and BT were effective in altering mood outcomes, and such improvement might be maintained at six months follow up [104]. Multidisciplinary pain management improved chronic pain patient's pain perception at 12 months follow up [109] and various aspects of QoL at six months follow up [107]. There was no firm conclusion for patient education for chronic LBP [103] and MPM did not show improvement in self-efficacy for chronic pain at 12 months follow up.

2.5 Comorbidities and symptomatology of chronic pain – a new direction of pain management

2.5.1 What is comorbidity?

Comorbidity means coexistence of several diseases and chronic conditions [14] or any two or more diseases occurring in the same person at the same time [110]. Examples of comorbidity may include comorbid migraine and gastric ulcer amongst patients who have neck pain or vice versa. Comorbidity in psychiatry can be further divided into heterotypic comorbidity, which means comorbidity from a different diagnostic disorder grouping such as depression and substance use disorder, or homotypic comorbidity, which means comorbidity from the same diagnostic disorder grouping such as alcohol drinking and use of marijuana [111].

2.5.2 What are the causes of comorbidity?

Figure 2.1 shows a schematic diagram of the causes and common risk factors of comorbidity.

The cause of comorbidity can be due to direct/indirect associations between the diseases [110], genetic susceptibility and family history [112], chance alone [110] or unknown of cause [113]. For example the association between cervicogenic headache and neck pain is a direct association of comorbidity, and the association between diabetes and cardiovascular disease is an indirect association of comorbidity. Genetic susceptibility and familiar history may explain some of the causes of comorbidity, but patients who present with two co-existing diseases may not share the same genetic susceptibility to the two co-existing diseases [112].

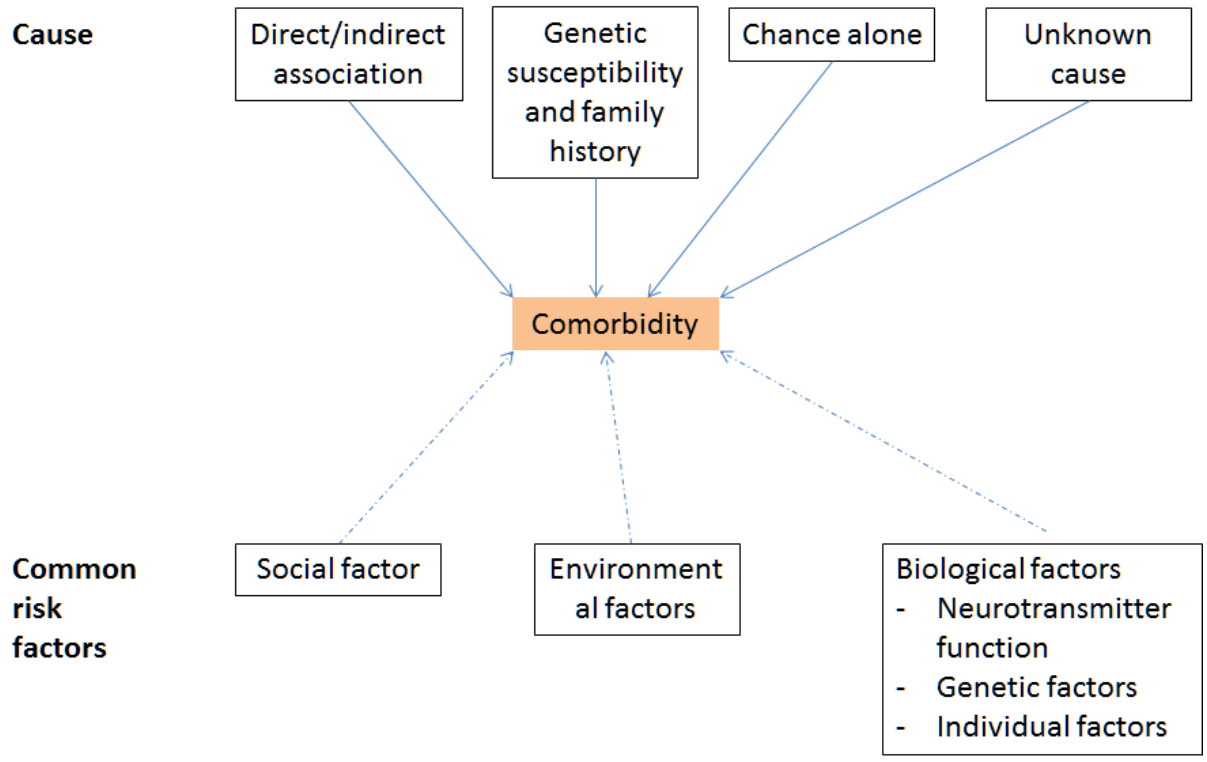


Figure 2.1 Causes and common risk factors of comorbidity

Common risk factors for more than one disorder may be the causes and the risk factors of both the disease and the comorbidity [113,114]. These common risk factors include social, environmental and biological factors [114]. Social and environment factors such as social disadvantage, e.g. social isolation and exposure to conflictual social relationships, have been shown to increase or be associated with the likelihood of different types of substance use disorder and mental disorders [115-117].

Biological factors can include the following categories:

- Neurotransmitter function: Some neurotransmitters act on the similar areas of the brain and share the same neurotransmitter system with the comorbidity [114]. Some neural substrates are similar in both mental disorders and substance use disorders [114].

- Genetic factors: Tsuang et al. found that twin males who abused any category of drugs were associated with increased probability of abusing any other category of drugs [115]. Kendler et al. investigated twin females and found genetics and family history were two probable factors for the association between major depression and cigarette smoking [118].

- Individual factors: Neuroticism was associated with substance use disorder and mental health issues [114].

Other than the above mentioned causes, there are still a lot of unknowns about the causes of comorbidity [113].

2.5.3 What are some comorbidities associated with chronic pain?

The evidence for comorbidities of chronic pain conditions has been documented in various reviews. Migraine increased the odds of getting depression, generalized anxiety disorder (GAD), and panic disorder [119,120]. Moreover, migraine even increased the odds of having bipolar disorder by 2.9-7.3 times [119]. Arthritis (defined as including arthritis, rheumatism, or other bone or joint diseases in the publication) in general was associated with increased odds of having depression (OR 1.39 95% CI 1.04-1.87) and GAD (OR 1.77 95% CI 1.04-3.02) [120]. Rheummatoid arthritis had the comorbidity of anaemia [121]. Fibromyalgia had psychiatric comorbidities such as anxiety, panic attacks, depression and post traumatic stress disorder (PTSD) [122], and was associated with the increased prevalence of obesity [123]. Furthermore, the incidence of depression was higher in chronic pain patients than in other medical illnesses [124].

Comorbidities of chronic neuropathic and non-neuropathic pains include hypercholesterolaemia [125], heart disease [125], disease of the digestive system [125], disease of musculoskeletal and connective tissue[125], insomnia [126], depression [126], and anxiety [126]. Moreover, post herpetic neuralgia patients experience chronic fatigue, anorexia, weight loss,

physical inactivity and insomnia, depression, and difficulties in concentration [124].

So far no SR has been conducted to specially examine the comorbidities of CMP.

2.5.4 What is symptomatology?

Symptomatology as defined by Mosby's medical dictionary is "the science of symptoms of disease in general or of the symptoms of a specific disease" [45]. For example, morning stiffness, red and swollen joints, and painful joints, are all symptoms of RA; pain in many joints is a symptom of fibromyalgia.

2.5.5 What are some common symptoms associated with chronic pain?

Examples of symptomatology of chronic painful diseases are listed in Table 2.8. As shown in Table 2.8, the symptoms of chronic painful conditions/diseases are not just pain alone. They involve musculoskeletal, dermatological, neurological, and gastroenterological symptoms and dosrders of the endocrine system, emotional and psychological disorder, and problems of the ear, nose, and throat.

Table 2.8 Common painful and non-painful symptoms and comorbidities of chronic painful conditions or diseases

Conditions / diseases	Painful symptoms	Some of the non-painful symptoms	Other comorbidity
Dermatomyositis	Muscle tenderness, multiple joints pain.	Reddish purple rash, symmetrical muscle weakness, muscle atrophy, difficulty in swallowing.	Raynaud's phenomenon
Sjogren's syndrome	Painful joints	Hypersensitivity to light, dry mouth as well as dryness in the mucous membrane such as in the nose, throat, bronchus, external genitalia and vagina.	Raynaud's phenomenon
Polymyalgia rheumatica	Muscle pain and stiffness in the muscles of the neck, shoulder blade, and pelvic region.	Muscle stiffness in the muscles of the neck, shoulder blade, and pelvic region. Weight loss, fever, depressiveness.	No comorbidity is mentioned
RA	Painful joints	Morning stiffness of the affected joints, red and swollen joints, forceless in	No comorbidity is mentioned

Conditions / diseases	Painful symptoms	Some of the non-painful symptoms	Other comorbidity
		the afternoon, poor appetite, general weakness, low grade fever, deformity of joints.	
Ankylosing spondylosis	Back pain	Low grade fever, fatigue, anorexia, weight loss.	Anaemia
Fibromyalgia	Tenderness to touch or pressure affecting joints and muscles, pelvic pain.	Depression or anxiety, fatigue, sleep problems (waking up unrefreshed), problems with memory or thinking clearly, irritable or overactive bladder.	Migraine or tension headaches, irritable bowel syndrome or gastroesophageal reflux disease, temporomandibular disorder (including symptoms of face or jaw pain, jaw clicking and ringing in the ears)

The information were extracted from The Merck Manual 18th Edition and the American College of Rheumatology website http://www.rheumatology.org/practice/clinical/patients/diseases_and_conditions/fibromyalgia.asp
RA: Rheumatoid arthritis

2.5.6 The implications of comorbidities and symptomatology on pain management, burden to the health care system, and QoL

As shown in the previous sections, chronic pain patients present with symptoms of more than just pain alone. Management for these patients requires inputs from a pain specialist, dermatologist, neurologist, gastroenterologist, endocrinologist, psychologist, psychiatrist, and ear, nose and throat specialists. The involvement of so many specialists creates a burden to the health care system. As mentioned by Access Economics, the cost of pain alone is already great [8], and managing these chronic pain patients will also incur costs involving the above mentioned specialist visits and treatments which increases health expenditure. One clinical trial looked at comorbid fibromyalgia amongst migraine patients [127]. Its results showed migraine prophylaxis improved the monthly flare up and pain threshold of fibromyalgia symptoms as well as analgesics usage ($p < 0.0001$) (the study did not provide numerical value/VAS for the percentage of reduction). This provides an example of how treating comorbidity reduced the overall burden of disease.

Comorbidities and symptomatology of chronic painful conditions/diseases include psychiatric issues, which affects the psychological well-being, and functional limitation of the person.

These directly or indirectly affect the patient's social network and social support and subsequently their ability to function as a normal person, i.e. impaired QoL. This concept is in line with Hartvigsen who proposed to view CMP together with its comorbidities and accompanying symptoms as the first line in diagnosis since the multiple painful sites occurred together with the co-existing symptoms [39].

2.5.7 Summary

Considering the impact of comorbidities and symptomatology, it is clear that when managing chronic pain, one should also manage the co-existing conditions and non-pain symptoms in order to provide an enhanced QoL. Comorbidity worsens physical disabilities [128], so if comorbidities and multiple non-pain symptoms are not managed concurrently, one may be unable to function as a normal person. The next section will introduce a medical system that concurrently focuses on patients' pain and non-pain symptomatology – CM.

2.6 Chinese medicine

2.6.1 What is CM

Chinese medicine has been in existence for a few thousand of years [129(p.1)]. It is the key medical system in ancient and modern China [130(p.4)]. Chinese medicine includes treatment the modalities of Chinese herbal medicine, acupuncture, moxibustion, cupping, exercise therapy, diet therapy, emotional therapy [130(p.766, 773)], and Tuina (Chinese therapeutic massage) [131(p.1)].

2.6.2 CM syndrome differentiation

In CM diagnosis, conditions are classified into main types of syndromes by utilizing the ancient theories and philosophy of Yin Yang and five elements, and the medical understanding of the function of the body organs (Zang-Fu), meridians, three Jiaos, "Wei, Qi, Ying, and Xue phases" and CM eight guiding principles [38]. Based on the pattern of symptoms and signs, a treatment principle is designed and applied to formulate the treatment [132(p.83-100)].

The CM Zang Fu organs have the same name as western medicine but focus more on the function of the organ than on the structure of the organ [133(p28-53)]. The CM Zang Fu organs and five elements have a close relationship which also correlates with other body parts, and emotions (Table 2.9). For example, the CM wood element is associated with the CM liver, the

CM gall bladder, the eye, tendons, and emotion of anger. When a person has red and painful eyes accompanied with excessive short temper, this person is said to have CM liver fire syndrome. Due to the interactions between the five elements, when the CM liver is in excess, as in this case, it will over control the earth element which is the digestive system represented by the CM spleen and CM stomach. Such person is prone to stomach pain, abdominal pain, or diarrhoea.

Table 2.9 CM five elements and their associated CM Zang Fu organs and other relationships

Five elements	Zang organs	Fu organs	Five sensory organs	Body tissues	Emotions
Wood	CM liver	CM gall bladder	Eye	Tendon	Anger
Five	CM heart	CM small intestine	Tongue	Vessels	Joy
Earth	CM spleen	CM stomach	Mouth	Muscle	Overthinking
Metal	CM lung	CM large intestine	Nose	Skin	Grief
Water	CM kidney	CM urinary bladder	Ear	Bone	Fear

Information extracted from [133(p20)]

Chinese medicine syndrome differentiation, also known as CM pattern identification, is a holistic approach to the CM diagnosis of conditions. The way CM views and differentiates conditions is by means of checking all the accompanying symptoms and signs. Taking the example of LBP (Table 2.10). If the LBP is aggravated by change in the weather such as a rainy day, then the CM pattern for this LBP is CM dampness retention pattern. If the LBP is sharp in nature, at a fixed location, worse at night and better during the day, then this LBP is CM blood stasis pattern. For CM dampness retention pattern, the treatment principle will be to remove the CM dampness; and for CM blood stasis pattern, the treatment principle will be to activate the CM blood circulation. The Chinese herbal medicine will vary significantly depending on the pattern whereas the acupuncture treatment does not vary as significantly as the Chinese herbal medicine.

Table 2.10 Chinese medicine patterns and treatments for LBP

Chinese medicine patterns	Signs and symptoms	Treatment principle	Acupuncture treatment	Chinese herbal medicine treatment
Cold dampness	Cold pain and heaviness in the low back area, difficult to turn the low back, gradual deterioration. Resting does not alleviate the pain and overcasting or rainy day aggravates the	Disperse cold and remove dampness, warm up	BL23 (Shenshu), BL40 (Weizhong), Huatuojiaji (extra point), Ashi point.	Modified Gan Jiang Ling Zhi Tang

Chinese medicine patterns	Signs and symptoms	Treatment principle	Acupuncture treatment	Chinese herbal medicine treatment
	pain. Thin greasy tongue coating, deep and slow pulse	and unobstruct the meridian	Moxibustion may be added.	
Damp heat retention	Painful heaviness in low back region accompanied with feverish sensation. The pain is aggravated in either hot or rainy days. Pain alleviated by movement. Red and scanty urine. Greasy yellow tongue coating. Rapid and soft pulse or rapid and taut pulse.	Clear heat and promote dampness removal via diuresis. Sooth the tendons and stop pain.	No listed treatment*.	Modified Si Miao Wan
Blood stasis	Sharp LBP at a fixed location, pain worse at night and better during the day. The mild case cannot bend their low back forwards and backwards, the severe case cannot turn on the side, refused to be touched at the tender area. Purple dark tongue body or accompanied with ecchymosis, uneven pulse. Some patients have history of trauma.	Activate blood circulation and resolve the stasis, regulate Qi and stop pain.	BL23 (Shenshu), BL40 (Weizhong), Huatuojiaji (extra point), Ashi point. Plus BL17 (Geshu), BL32 (Ciliao)	Modified Shen Tong Zhu Yu Tang
CM kidney deficiency	Low back ache, prefers to be touched and pressed on the painful area, weakness in knee and leg, worse after exertion and better after bed resting, often occurs repetitively. **For Yang deficiency:** patient will present with abdominal spasm, pale complexion, cold limbs, fatigue, pale tongue, deep and thready pulse. **For Yin deficiency:** patient will have insomnia, irritability, dry mouth and throat, malar flush, feverish sensation in the palms and soles, red tongue with little coating, taut, thready, and rapid pulse.	For Yang deficiency, warm and tonify CM kidney Yang. For Yin deficiency, nurture and tonify CM kidney Yin.	BL23 (Shenshu), BL40 (Weizhong), Huatuojiaji (extra point), Ashi point. CM kidney Yang deficiency: Add and apply moxibustion on GV4 (Mingmen), and Yaoyan (Extra point) CM kidney Yin deficiency: BL52 (Zhishi), KI3 (Taixi)	For Yang deficiency: modified You Gui Wan. For Yin deficiency: modified Zuo Gui Wan.

LBP: low back pain
Information extracted from Chinese medicine internal medicine [134(p266-267)] and Lecture notes for KP610/COTH1040: Acupuncture practice 1 (Techniques and treatment) [135]
* There was no acupuncture treatment for CM damp heat retention pattern in LBP even after searches in other six textbooks/literatures [136(p91)137(p291-294.689)138(p362-364) 139-141].
CM: Chinese medicine
LBP: Low back pain

There is a CM pattern identification called the CM eight guiding principles [38]. The CM eight guiding principles differentiate the presentation of symptoms into Exterior/Interior, Cold/Heat, Deficiency/Excess, and Yin/Yang types (Table 2.11). Exterior pattern symptoms include symptoms of fever and chills. These symptoms are the typical symptoms of the exterior pattern. Interior pattern symptoms include symptoms pertaining to the interior part of the body which can include high grade fever, irritability, thirst, and constipation. Cold pattern symptoms include cold limbs, aversion to cold and preference for warmth, and loose stool. Heat pattern symptoms include the opposite symptoms to the cold pattern e.g. constipation, fever, prefers cold temperature, thirst with preference for cold drinks. Deficiency pattern symptoms pertain more to weakness e.g. lassitude, fatigue and excess pattern symptoms pertain to higher temperature, irritation, and dryness, e.g. fever, irritability, and constipation. Yin and Yang patterns are the overarching patterns that dominate all the other six patterns. Yin pattern symptoms include symptoms of a more Yin nature which are similar to cold, interior, and deficient and may include fatigue, tiredness, forceless, feeble voice. Yang pattern symptoms include symptoms opposite to the Yin pattern symptoms and include fever, hot skin, coarse voice, and constipation. These eight patterns exist alone or in combination e.g. exterior excess cold pattern, interior excess heat pattern, or interior deficient cold pattern.

Table 2.11 CM eight guiding principles symptom presentations

CM eight guiding principles patterns	**Symptoms**
Exterior	Fever, chills, headache and body aching, thin white tongue coating, floating pulse. May have a stuffy and running nose, itchy or sore throat, and cough.
Interior	High grade fever, irritability, delirium, thirst, abdominal pain, constipation or diarrhoea with nausea and vomiting, scanty red urine, yellow or white thick greasy tongue coating, deep pulse.
Cold	Aversion to cold and prefers warmth, pale complexion, cold limbs, sleeping with body curled up, bland taste in the tongue without thirst, clear and thin phlegm/saliva/nasal discharge, clear and profuse urine, loose stool, pale tongue with white coating and slippery texture, slow or tense pulse.
Heat	Fever and prefers cold temperature, thirsty with preference for cold drinks, red eyes and face, irritability and restlessness, yellow thick phlegm/nasal discharge, vomiting of blood or bleeding nose, red and scanty urine, dry hard stool, yellow and dry tongue coating, red tongue body, rapid pulse.
Deficiency	Pale or withered complexion, lassitude, fatigue, palpitations and shortness of breath, cold limbs and body, spontaneous sweating, incontinence, pale fat and delicate tongue body, deficient deep and slow pulse. Or “heat in the chest, palm, and soles”, emaciation, malar flush, dry mouth and throat, night sweating, tidal fever, red tongue

CM eight guiding principles patterns	Symptoms
	with little coating, deficient thready and rapid pulse.
Excess	Fever, abdominal pain and refusal to be touched, chest stuffiness, irritability, maybe coma with delirious speech, rapid coarse breathing, excessive phlegm and saliva, constipation or dysentery, tenesmus, difficulty in urination, dripping or painful urination, tight and puffy tongue, thick greasy coating, forceful pulse.
Yin	Dark complexion, fatigue, heaviness sensation in the body, sleeping with body curled up, cold limbs and body, tired and forceless, feeble voice, poor appetite, bland taste in the mouth, without thirst, profuse and clear urine, pale puffy and delicate tongue body, deep slow or weak thready and uneven pulse.
Yang	Red complexion, fever, skin feels hot, irritability, coarse voice or manic speech, coarse breathing, wheezing, constipation, crimson tongue body, yellow black tongue coating with thorns. Floating, rapid, roaring, big, slippery, excess pulse.

Information extracted from CM diagnosis by Deng et al. [38].

2.6.3 How does CM view and differentiate CMP

Chronic musculoskeletal pain is not a CM term. The closest CM concept of CMP is Bi syndrome, which means a blockage of Qi and Blood flow in the painful area in the muscles, tendons, bones or joints [132(p887)]. This interrupted flow of Qi and CM blood is associated with three factors: 1) invasion of external pathogens such as wind, cold, dampness, or damp-heat, 2) retention of pathological products, including CM phlegm and/or CM blood stasis, and 3) constitutional deficiency [132(p887-888)].

Figure 2.2 shows the pathogenesis of Bi syndrome. When a person is invaded by external pathogens, his or her constitution can be normal or weak. If the person is weak and not able to expel these external pathogens, these pathogens will then stay in the meridians, joints or muscles and mingle together with dampness and finally form Bi syndrome [132(p888)]. Alternatively when the external pathogens remain in the meridians, joints, or muscles, they will impede the Yang Qi flow in the meridian and cause the CM blood flow to stagnate and phlegm to form [132(p888)]. The stagnated CM blood and phlegm will further impede the flow of Yang Qi and subsequently make the local area malnourished [132(p888)]. Over a period of time, these external pathogens will enter into the organs and form the Bi syndrome of the five CM Zang organs, the CM liver, CM heart, CM spleen, CM lung, and CM kidney, especially the Bi syndrome of the CM heart organ [132 (p888)].

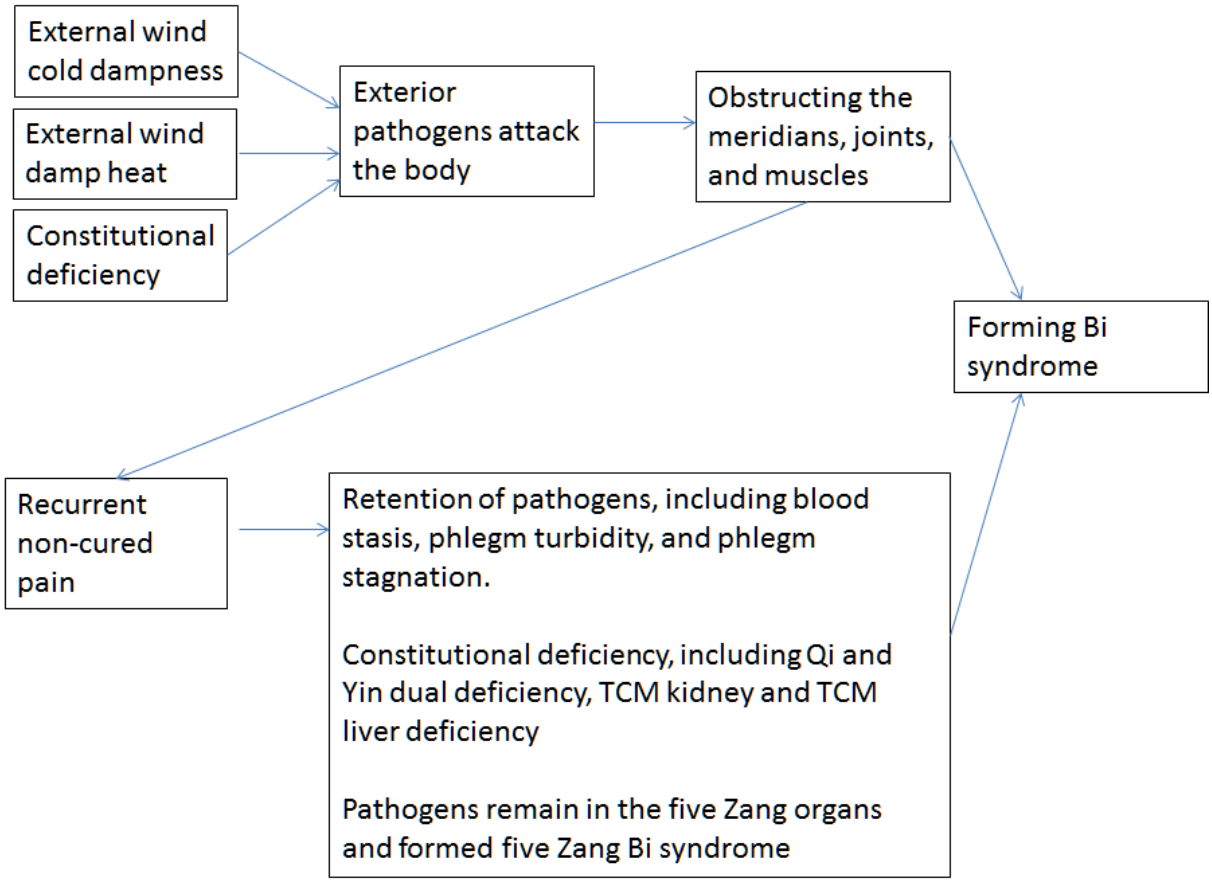


Figure 2.2 Pathogenesis of Bi syndrome

CM categorises Bi syndrome into different types (see Zhang et al. [134(p266-267)]. These types are listed in Table 2.12.

Table 2.12 Diagnosis of different types of Bi syndrome and their associated acupuncture and CM herbal treatments

CM Bi syndrome	Symptoms	Acupuncture treatment	CM herbal treatment
Wind dampness heat Bi syndrome	Red, swollen, hot, and painful joints, better with cold temperature, dislikes being touched, may involve more than one joint, often accompanied with fever, aversion to wind, thirst, and irritability. Dry yellow tongue coating, slippery rapid pulse.	GV14 (Da Zhui), LI11 (Qu Chi)	Modified Bai Hu Gui Zhi Tang
Wandering Bi syndrome	Limbs and joints have pain that moves around, difficult to extend/flex the joint, aversion to wind, fever, thin white tongue coating, floating pulse.	BL12 (Feng Men), BL17 (Ge Shu), BL18 (Gan Shu) + moxibustion	Modified Fang Feng Tang
Painful Bi syndrome	Severe limb and joint pain at a fixed location, pain alleviated by warmth and aggravated by cold temperature, difficulty	BL23 (Shen Shu), CV4 (Guan Yuan) + moxibustion	Modified Wu Tou Tang

CM Bi syndrome	Symptoms	Acupuncture treatment	CM herbal treatment
	in flexion/extension of the joint, local skin not red, and not warm to touch. Thin white tongue coating, thready taut pulse.		
Fixed Bi syndrome	Ache in limbs and body, may have swelling in the joints, pain at fixed location, heaviness in the limbs, difficulty to move, as well as numbness in the affected skin. Greasy white tongue coating, soft and even pulse.	BL20 (Pi Shu), ST36 (Zu San Li), SP9 (Yin Ling Quan) + moxibustion	Modified Yi Yi Ren Tang

For acupuncture treatments, on top of the aforementioned prescriptions, the following prescriptions are for pain and/or dysfunction at each anatomical location:
Shoulder: SJ14 (Jian Liao), LI15 (Jian Yu), SI10 (Nao Shu)
Elbow: LI11 (Qu Chi), LI4 (He Gu), SJ10 (Tian Jing), SJ5 (Wai Guan), LU5 (Chi Ze)
Wrist: SJ4 (Yang Chi), SJ5(Wai Guan), LI5 (Yang Xi), SI4 (Wan Gu)
Spine: GV26 (Shui Gou), GV12 (Shen Zhu), GV3 (Yao Yang Guan)
Thigh: GB30 (Huan Tiao), GB29 (Ju Liao), GB39 (Xuan Zhong)
Hip: BL54 (Zhi Bian), BL36 (Cheng Fu), SP9 (Yin Ling Quan)
Knee: ST35 (Du Bi), ST34 (Liang Qiu), GB34 (Yang Ling Quan), GB33 (Xi Yang Guan)
Ankle: BL62 (Shen Mai), KI6 (Zhao Hai), BL60 (Kun Lun), GB41 (Qiu Xu).
Source of information [134(p266-268)136(p91)]

Another classification method of Bi syndrome depends on the season or month of the year it occurs. If the Bi syndrome occurred during winter, spring, summer, June, or autumn, they are called bone Bi syndrome, tendon Bi syndrome, pulse/vessel Bi syndrome, muscle Bi syndrome, or skin Bi syndrome respectively [142(p. 268)].

After identifying the types of Bi syndrome, the CM pattern is then differentiated based on the accompanying symptoms and signs. Based on the textbook information by Wang et al. [132(p890-895)], there are ten CM patterns for Bi syndrome (Table 2.13). Subsequently, the principle of treatment is designed based on the CM pattern and the treatment will be given based on the treatment principle [132(p890-895)]. When the CM patterns differ, their treatment principle and the treatment rendered also differ. The treatment principle for “Cold dampness Bi obstruction (寒湿痹阻)” and “Damp heat Bi obstruction (湿热痹阻)” are completely different. Cold dampness Bi obstruction requires warming up the meridian and dispersing the cold whereas Damp heat Bi obstruction requires clearing heat and removing dampness. If the wrong treatment is prescribed, treatment recovery may not be possible, and symptom deterioration is expected.

Table 2.13 CM pattern, treatment principle, and Chinese herbal medicine treatment for Bi

syndrome

CM pattern	Symptoms	Treatment principle	Chinese herbal medicine treatment
Wind dampness Bi obstruction (风湿痹阻)	Aching, soreness, heaviness in joints and muscles, pain wanders around and occurs mainly in the major joints, swollen joints or muscles, inflexibility of joints, numbness on the skin/muscles. Symptoms often begin with exterior wind cold pathogen attack and fever.	Remove cold and eliminate dampness, unobstruct the meridian and stop pain	Modified Juan Bi Tang
Cold dampness Bi obstruction (寒湿痹阻)	Cold pain, heaviness, and pain at fixed location at the joints or limbs. Worse at night and better during the day. Pain aggravated by cold temperature and alleviated by warm temperature, or swelling at the painful sites, the skin is not red and does not feel feverish upon touching, no inflexibility of the joints.	Warm the meridian and disperse the cold, remove dampness and unobstruct the meridian	Modified Wu Tou Tang
Cold and heat mixture (寒热错杂)	Swelling, feverish painful sensation at the limbs/muscle/joints. Aversion to cold at the pain site, or the patient feels a feverish sensation at the pain site but is not hot upon touching. The skin may have rashes but the extremities may turn blue when encountering cold temperature. Inflexibility of the joints which may be alleviated with warmth. The joints maybe stiff, deformed. The patient may feel feverish without a feverish sensation upon touching, fever with chills, feverish sensation and wants to cover up with sheets, thirsty with preference for hot drinks, or spontaneous sweating with cold body.	Warm the meridian and disperse cold, clear heat and remove dampness	Modified Gui Zhi Shao Yao Zhi Mu Tang
Damp heat Bi obstruction (湿热痹阻)	Red, hot, swollen, and painful muscles or joints, accompanied with heaviness sensation. May have fever, thirsty without craving for drinks, irritable, dark yellow urine, inflexibility of joints, difficulty with walking, or accompanied with rashes in joints.	Clear heat and remove dampness, eliminate stagnation and unobstruct the meridian	Modified Xuan Bi Tang and Dang Gui Nian TongTang
Heat toxin Bi obstruction (热毒痹阻)	Crimson feverish sensation at the joints, extremely painful and refuses to be touched. Feverish sensation upon touching and better with cold temperature. Accompanied with high body temperature and excessive thirst, or subcutaneous nodule, inflexibility of joints, red complexion, sore throat, red urine, constipation, may have delirium.	Clear heat and relieve toxin, cool blood and unobstruct the meridian	Modified Xi Jiao Tang
Static blood	Pins and needles sensation at the	Activate blood	Modified

CM pattern	Symptoms	Treatment principle	Chinese herbal medicine treatment
Bi obstruction (瘀血痹阻)	joints/muscles at a fixed location. The pain lasts for a long time, the painful area refuses to be touched. There may be ecchymosis or hard nodule at the local swelling, or dark complexion, dry and lusterless skin, dry mouth without preference to drink.	circulation and resolve stasis, soothe the tendon and unobstruct the meridian	Shen Tong Zhu Yu Tang and Huo Luo Xiao Ling Dan
Phlegm turbidity Bi obstruction (痰浊痹阻)	Swollen joints, numb and painful, or accompanied with phlegm nodule, dizziness and vertigo, head heaviness feels like a band around the head, stuffiness in the chest and fullness in the epigastrium, poor appetite with nausea, vomits out phlegm and froth, swollen eye lid.	Resolve phlegm and activate Qi circulation, unobstruct the meridian and stop pain.	Modified Ban Xia Bai Zhu Tian Ma Tang and Yang He Tang
Phlegm stasis Bi obstruction (痰瘀痹阻)	Chronic pain, pins and needles sensation in the joints/muscles at a fixed location, or dark purple swollen joints/skin, hard on palpation, numb and heavy sensation in the extremity or accompanied with deformed and stiff joints. Inflexible joints, there may be ecchymosis or hard nodule. Dark complexion, swollen eye lid, or stuffiness in the chest with copious phlegm.	Activate blood circulation and resolve stasis, resolve phlegm and unobstruct the meridian	Modified Shuang He San
Deficiency of both Qi and Yin (blood) (气阴(血)两虚)	Painful, swollen, stiff, deformed bone and joints, may have tendon and muscle spasm. Thin body build, low grade fever, shortness of breath and weakness, palpitation, easily sweats, or muscle aching, pain and weakness. Symptoms aggravated after exercise. Pale nails, dizziness and vertigo, poor appetite with loose stool. Dry mouth without preference to drink, lusterless or numb skin, nodules, or ecchymosis in the skin.	Benefit Qi and nurture Yin, activate blood circulation and unobstruct the meridian	Modified Sheng Mai San and Huang Qi Gui Zhi Wu Wu Tang
Deficiency of both CM liver and CM kidney (肝肾两虚)	Chronic Bi syndrome not cured, swollen and painful joints, tendons and muscles, stiff and deformed. Muscle becomes thin, and accompanied with low back and knees soreness and weakness. Patient may not be able to stand up and extend their neck (脊以代头,尻以代踵)*, aversion to cold and prefers to sleep, cold extremities, or steaming bone sensation, spontaneous sweating and night sweating, thirsty without preference to drink or does not drink much.	Tonify CM liver and CM kidney	Modified Du Huo Ji Sheng Tang

*This symptom is described as the patient can sit only but cannot walk. The patient can only lower the head but not lifting the head up. The patient's coccyx is touching the ground and his cervical bones are slanting down and his spinal vertebrae are springing up.

According to the textbook information, there exist some discrepancies between textbooks on the Bi syndrome CM patterns and their treatment [134(p266-268)132(p890-895)]. Such differences are due to different experts having been involved in compiling the textbooks. This creates a problem in standardising CM patterns for Bi syndrome.

2.6.4 CM understanding of the symptomatology of chronic pain

Chinese medicine views the health of a person holistically [143(p28)]. All the parts in the body and medical conditions are considered related to one another via the relationships between the CM Zang Fu organs, the meridians, or the inter-relationship between the five elements [143(p134-147,247-255, 268-315)]. These relationships are assessed when diagnosing the CM pattern of a condition. The aim of CM pattern identification is to identify the pattern of symptom presentation, and the mechanism of the illness – including the pathogenesis and sometimes the causes. Symptoms, signs, and conditions that come under the same CM pattern can happen concurrently. For example: LBP and tinnitus. These two symptoms are related to the low back and ear. The low back region in CM is the house of the CM kidney. The ear is the opening orifice of the CM kidney. If both symptoms occur concurrently, this pattern is considered as CM kidney deficiency. The locations of these symptoms can be linked together by the distribution of Foot Tai Yang bladder meridian, which is related to the CM kidney via the water element relationship of the five elements (see Table 2.9 and Figure 2.3). Another example is headache, sore and red eyes, tinnitus, and pain in the lower rib area. The temple area and the ear are where the gallbladder meridian passes (see Figure 2.4), and the lower rib area is where the CM liver meridian passes. The eyes are the opening orifices of the CM liver. The CM liver and CM gallbladder are a pair belonging to the wood element (Table 2.9). If the above symptoms occur concurrently, this pattern is called CM liver Yang Upsurging.

As explained before, the body parts and CM organs are related to one another through the meridian system. For instance, the spreading of LBP to the upper back, neck, and head, or spreading to the hips and knees could be explained by the obstruction of the Qi and CM blood flow in the Foot Tai Yang bladder meridian as this meridian travels from the head to the feet [144(p140)] (Figure 2.3).

Apart from the anatomical locations and meridians, the CM organs also have their associated emotions. The five CM Zang organs (the solid internal organs), include the CM liver, CM heart, CM spleen, CM lung, and CM kidney. These are associated with anger, joy, overthinking, grief, and fear (Table 2.9, p. 33) [133(p20)]. In the case of the CM liver Yang upsurging pattern which involves the CM liver, this pattern could also present with grumpiness or anger due to there being excessive Yang.

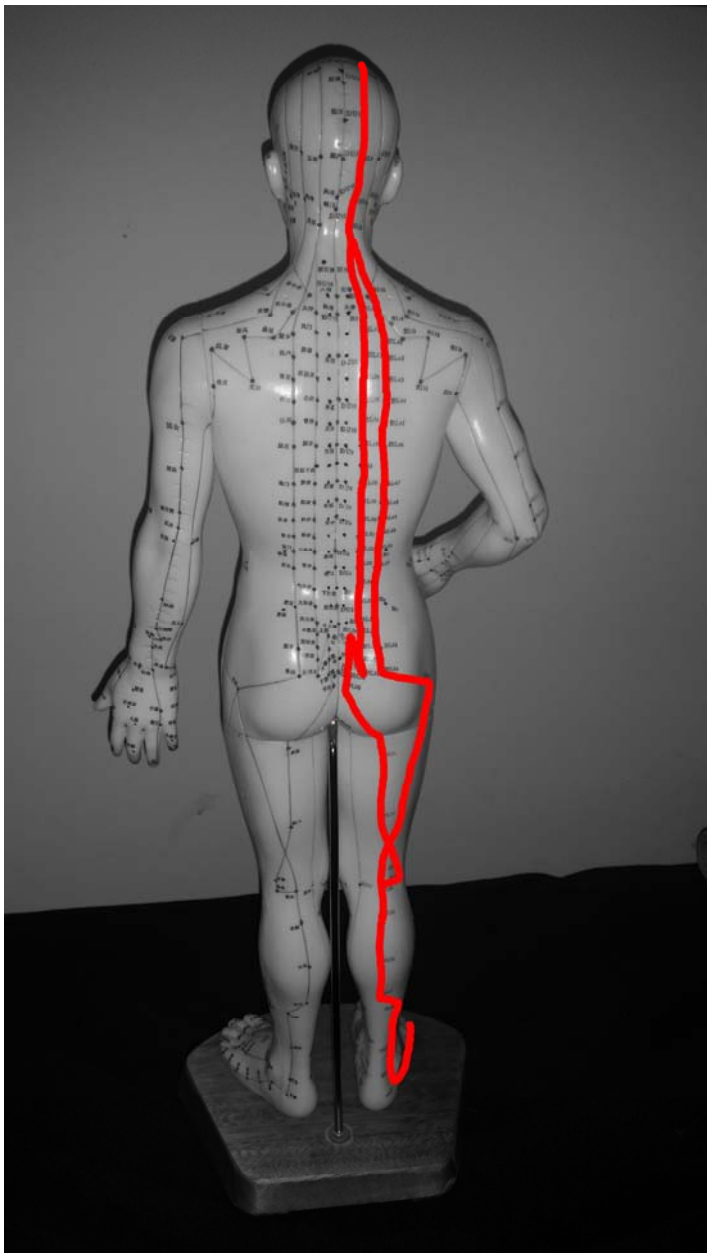


Figure 2.3 The distribution of Foot Tai Yang bladder meridian (marked in red)

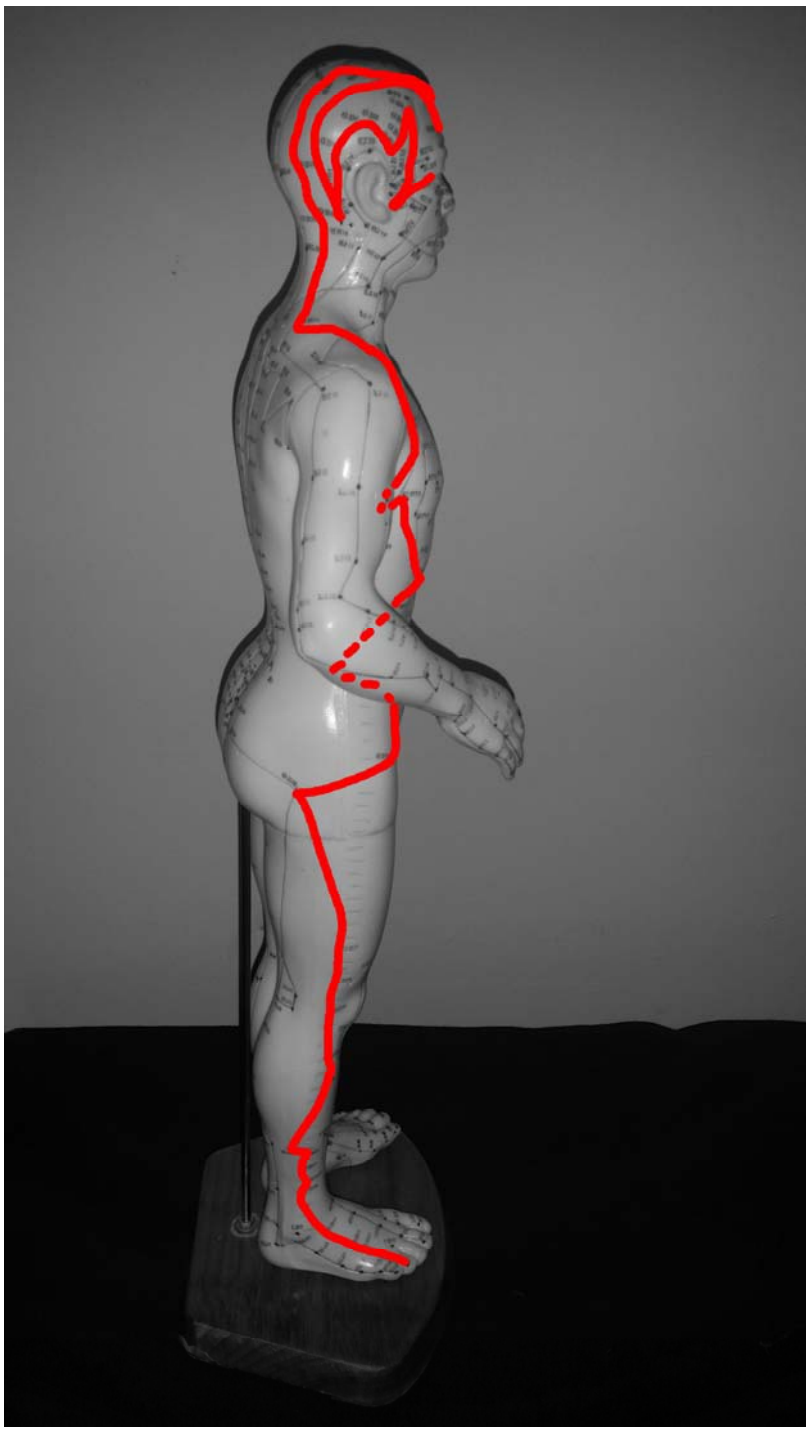


Figure 2.4 The distribution of Foot Shao Yang gallbladder meridian (marked in red, dotted line indicates meridian path covered by arm)

Overall, the symptomatology of CMP plays an important part in CM pattern identification. These seemingly unrelated symptoms may influence the resultant CM pattern identification and consequently the principle of treatment and the treatment rendered.

2.6.5 CM understanding of the side effects of pharmacotherapy

Based on CM understanding, some of the side effects and withdrawal symptoms of OM can be categorised according to the CM heat or cold patterns. Side effects such as itching, urticaria, constipation, sleep disturbances and restlessness are heat type symptoms (Table 2.14) whereas the opposite cold type side effects include reduced sex drive (Table 2.14). The withdrawal symptoms of OM can also be categorised into heat or cold patterns (Table 2.14). In addition, there are some withdrawal symptoms such as anxiety, and increased tearing which cannot be categorised simply into either CM heat or cold patterns.

Table 2.14 Side effects and withdrawal of OM categorised by CM heat and cold patterns

CM patterns	Side effects of OM	Withdrawal symptoms of OM
CM heat pattern	itching around nose, and urticaria, constipation, delayed gastric emptying, sleep disturbance, behavioural restlessness	Agitation, insomnia
CM cold pattern	nausea and vomiting and reduced sex hormone	Muscle aches, runny nose, abdominal cramping, diarrhoea, nausea, vomiting.

Information extracted from Schumacher et al. [76] and MedlinePlus [145].
OM: Opioid medication

These heat and cold patterns contain symptoms of the opposite nature. The heat pattern contains symptoms that are more hot, agitating, irritable, and dry. These symptoms are also considered to be Yang in nature. The cold pattern, on the other hand, contains symptoms that are more cool, painful, watery, sedative, and motiveless. These symptoms are more Yin in nature.

2.6.6 CM pattern studies of chronic pain

There were limited studies examining the CM patterns of CMP. In the lumbar disc protrusion study, the confirmed disc protrusion cases by computed tomography were 42 for the group with traumatic history, and 96 for the group without traumatic history. For the group with traumatic history, 36 of them (86.6%) were diagnosed with CM blood stasis pattern, and the remaining six (14.2%) were diagnosed with CM deficiency pattern. The CM deficiency pattern included CM Qi and blood deficiency pattern, CM liver and CM kidney deficiency pattern, or “acute sprain, strain, or contracting wind cold dampness pathogen during the

recovery period after chronic pain or major illness". For the group without traumatic history, 60 of them (62.5%) were diagnosed with CM cold dampness retention pattern, 32 of them (33%) were diagnosed with CM damp heat and phlegm retention pattern and the remaining four (4.2%) were diagnosed with CM deficiency pattern. Such a finding indicated a different view and understanding of LBP which was not limited by the structural pathology as indicated by computed tomography.

2.7 Acupuncture and pain management

2.7.1 Mechanisms of acupuncture

Commonly there are a few forms of acupuncture, depending on the methods of acupuncture point stimulation. Stimulating acupuncture points with filiform needles alone is called manual acupuncture. When electrical current is delivered with an electroacupuncture (EA) machine attached to the inserted needles, this form is called EA [146]. Acupuncture points can also be stimulated with laser, which is called laser acupuncture [147](p112); with warmth via applying moxibustion on top of the inserted needles, called warm needling [147](p55); with three edge needles to draw blood for the therapeutic purpose, called three edge needling [147](p61). Acupuncture can also be classified based on the types of points stimulated or the selection of treatment points, and this includes body acupuncture, eye acupuncture, ear acupuncture, scalp acupuncture, hand acupuncture, wrist and ankle acupuncture, and foot acupuncture [148](p100-117) .

There are currently six scientific theories for the mechanisms of acupuncture analgesia [149]: 1) Natural opioid substance – endogenous opioid substance, 2) gate control theory, 3) endogenous corticosteroid release, 4) myofibrillary entanglement, 5) local blood flow, and 6) mesolimbic loop of analgesia.

2.7.1.1 Natural opioid substance – endogenous opioid peptides

Opioid substances including endorphin/endomorphin, and encephalin are activated by 2Hz EA while dynorphin is activated by 100 Hz EA stimulation [150]. Endorphin and encephalin are potent analgesics for musculoskeletal pain while dynorphin is a potent analgesic for visceral pain [149].

2.7.1.2 Gate control theory

Melzack et al. [151] proposed the gate control theory in 1965 which stated that pain signals sent through the small diameter fibres (C fibre) were inhibited by the substantia gelatinosa which received input from the large diameter fibres (Aβ). Acupuncture activates Aβ fibres which then inhibit the transmission of pain signals through Aβ C fibres. This explains how local point needling at the pain site might relieve painful sensations.

2.7.1.3 Endogenous corticosteroid release

Adrenocorticotrophic hormone is elevated after EA treatment [152]. This suggests EA activated a stress response which is related to the release of the endogenous corticosteroids. Endogenous corticosteroids are well known to treat pain related conditions [153].

2.7.1.4 Myofibrillary entanglement

Trigger point injection has been used for treatment of painful conditions [154(p187-341)]. Acupuncture may relax the muscle fibres within the tissues. This effect of acupuncture on painful points is thought to be similar to trigger point injection into the painful trigger points [149].

2.7.1.5 Local blood flow

Acupuncture treatment causes a small trauma to the body. Such treatment may increase the blood flow to the area surrounding the needles consequently triggering a healing process [149].

2.7.1.6 Mesolimbic loop of analgesia

Dopamine plays a crucial role in pain coping response and avoidance [155]. Chronic pain impairs the mesolimbic dopamine activity that interferes with motivated behaviours [155]. Acupuncture treatment can modulate the mesolimbic dopamine neurons and subsequently reset the pain-modulating pathway [156].

2.7.2 Acupuncture treatment

After a CM pattern identification is made, the acupuncture points may be selected for treatment. The point selection is based on 1) local and distal points, 2) the diseased meridian, 3) the other involved meridians, 4) empirical points, and 5) Ashi points, which literally means

"ouch" points, and refers to points that are painful to touch or pressure [136(p15)]. For example, in Bi syndrome due to cold stagnation at the lumbosacral joints, the points selection includes local points such as Shenshu (BL23), distal points such as Weizhong (BL40) and Guanyuan (CV4), and moxibustion to disperse the cold and warm up the meridian along the spine from Dazhui (GV14) to Yaoshu (GV2), and the empirical point Renzhong (GV26) for LBP (Table 2.15).

Table 2.15 Acupuncture treatment for Bi syndrome due to cold stagnation at lumbosacral joints

Types of Bi syndrome	**Local point**	**Distal point**	**Diseased meridian points**	**Empirical points**
Bi syndrome due to cold stagnation at lumbosacral joints	Shenshu (BL23)[am], Dachangshu (BL25), Mingmen (GV4), Baliao (BL31-34)	Guanyuan (CV4) [am], Weizhong (BL40)	Moxibustion* along the spine from Dazhui (GV14) to Yaoshu (GV2)	Renzhong (GV26)
Function of the points.	Shenshu (BL23) and Guanyuan (CV4) to warm up Yang Qi and benefit the Qi, expel the cold pathogen. Moxibustion* along the spine from Dazhui (GV14) to Yaoshu (GV2). These points alone with the other local points, including Shenshu (BL23)[am], Dachangshu (BL25), Mingmen (GV4), and Baliao (BL31-34), were to regulate the meridian, activate Qi and blood, expel the pathogen and pain. Weizhong (BL40) is a well known point for LBP. Renzhong (GV26) can be used to activate the Qi in the Du meridian which runs from just anterior to the coccyx going up the spine alone the mid line of the back, back of the head, top of the head, front of the head, and ends at the philtrum.			

* Moxibustion is a heat therapy by burning mugwort on or close to the skin in order to disperse cold, eliminate dampness, nourishing Qi or warming Yang [157(p402)].
LBP: Low back pain
[am:] to apply acupuncture and moxibustion together.

Currently there is no defined acupuncture treatment frequency. Acupuncture treatment frequency varies from once a day to once a month [158]. A SR investigated different acupuncture regimens found two extreme frequencies were employed: 1) once to twice per week and 2) five to six times per week [159]. There is currently no consensus on the better treatment frequency although Yuan et al. pointed out there may be a dose response for the controlled acupuncture trials conducted in China where daily acupuncture treatment per week are normally applied and authors reported 100% favouring acupuncture treatment over the controls [159].

2.7.3 Acupuncture in pain management and acupuncture treatment based on CM patterns

Acupuncture, as described in Chapter 2.4.2.2 (p. 21), has shown effectiveness for painful conditions and been recommended by the USA AHRQ guidelines for painful conditions. Many of the SR identified acupuncture to be more effective than no intervention [91,92,94,160], sham acupuncture [36,91,161], inactive treatment (defined as sham TENS) [91], or as effective as other active intervention [92]. However, another meta-analysis found no difference between acupuncture and sham acupuncture [162]. One possible explanation for SRs not showing efficacy of acupuncture was heterogeneity amongst the trials [163]. Such heterogeneity may be due to the fact that trials did not consider the individual CM patterns of the participants. As described in Yang et al. [162], although the included trials selected points based on the acupuncture literature and CM theory, there was no point selection based on the CM patterns of the individual patients.

To date, knowledge of the CM patterns of CMP based on clinical data is still lacking. As indicated in Table 2.12, different acupuncture points as well as the utilisation of moxibustion were used for different CM patterns. The acupuncture treatment should be based on the CM pattern. As shown in the SRs where there was no difference or very small effect between acupuncture and sham acupuncture [37,94], none of the included studies treated the participants based on CM patterns. Another large acupuncture study (n=302) on migraine that showed no difference between acupuncture and sham acupuncture did not treat participants based on CM patterns [164]. It is important to design acupuncture trials that treat participants based on CM pattern.

2.7.4 Problems in current acupuncture research

As described in Chapter 2.6.3 How does CM view and differentiate CMP (p. 36), CM views the body and diagnoses the condition/disease with its own unique theory and interpretation. Treatments for different kinds of CM patterns also differ (Table 2.12). It is not a surprise to find poor results when using the same acupuncture protocol for a given condition without further identifying the suitable CM pattern for such acupuncture protocol. It is important to identify the CM pattern of the condition and individualise the acupuncture treatment based on the CM pattern, as is routinely done in clincal practice, to achieve the optimal result.

In order to identify the CM pattern, it is important to standardise the procedure of CM pattern identification. The first step is to have a consistent consultation procedure which can be achieved using a CM questionnaire [165]. Subsequently, the CM pattern reflecting the reality of a given condition, instead of being based on expert opinions as in the textbooks, should be identified. Then the acupuncture protocol for the given condition can be divised.

There is a need to fill this knowledge gap of CM pattern in reality in order to improve the quality of acupuncture clinical trials.

2.8 Chapter summary

This chapter reviewed the current literature regarding CMP, management of CMP, comorbidities and symptomatologies, the CM views of CMP, the principles of CM syndrome/pattern identification and acupuncture in pain management. The next chapter will examine the current knowledge of comorbidities and symptomatologies of CMP through a SR.

3. Systematic review on comorbidityies and accompanying symptoms associated with CMP conditions

3.1 Introduction

Painful conditions come with comorbidities and accompanying symptoms such as depression and anxiety [166], migraine [167], and neck pain [168]. Such accompanying illnesses/symptoms have huge implications for healthcare services and costs [169], such as increased physician visits, use of more medications, and are more likely to be hospitalised than people without accompanying illnesses/symptoms [170(p21,23)]. Research also shows that when a person has five or more chronic conditions, the health cost, which is 14,768 USD/capita health care spending, is almost 15 times more than for a person having no chronic conditions and five times more than for a person having only one chronic condition [170(p17)]. Moreover, comorbidities affect choice of treatment. For instance, when patients have comorbid peptic ulcer, NSAIDs are less likely to be prescribed; and when patients have comorbid hypertension, physical therapy (undefined in the publication) is less likely to be prescribed [171]. The overall comorbidities/accompanying symptoms of CMP are not fully understood. This SR assesses the current literature on comorbidities/accompanying symptoms of CMP. The aims of the SR were to identify 1) the types of comorbidities/accompanying symptoms of CMP; 2) the percentages of comorbidities/accompanying symptoms in CMP; and 3) the association between CMP and comorbidity/accompanying symptoms of CMP.

3.2 Method

3.2.1 Selection criteria

Types of study: cross-sectional, prospective cohort or clinical trial studies that described comorbidities and/or accompanying symptoms of CMP were included. Studies might apply a survey, questionnaire, or interview to obtain the data. Reviews, retrospective data from government or private health insurance databases, retrospective studies, and studies focused on non-musculoskeletal pain were excluded.

Types of participants: All participants with CMP were considered regardless of age, gender, or ethnic group. Chronic musculoskeletal pain were defined as musculoskeletal pain lasting for more than three months regardless of the location of musculoskeletal pain. Such CMP might include chronic SP, arthritis, and widespread pain. Studies that included CMP due to

cancer/tumour/metastatic diseases were excluded. Studies that reported CMP as a comorbidity/accompanying symptom of other illnesses were also excluded.

Types of comparison group: The comparison group were general population without the studied CMP. In an epidemiological/percentage study, there was no comparison group required. Studies that compared one kind of CMP to another kind of acute/chronic musculoskeletal pain were excluded.

Types of interventions: No specific intervention was the interest of this study. Only baseline data of clinical trials were extracted if the baseline included the epidemiological/percentage data needed.

Types of outcomes: Included studies reported comorbidities, accompanying symptoms, or related findings. Studies that reported musculoskeletal pain without specifying its location (e.g. back pain, or neck pain) were excluded.

Language was restricted to both English and Chinese. Publications in other languages were excluded.

3.2.2 Search strategy for identification of studies and study selection

Search strategies for identifying studies included

1) Databases: PubMed, CINAHL, EBSCO, PsycInfo, Cochrane library, and SCOPUS were searched from inception to 13/05/2015.

2) When the required data was not found in the publication, the authors were contacted.

3) References of the selected papers and reviews were searched.

Search terms used in PubMed were included in Table 3.1. Similar search terms were used in other databases.

Table 3.1 Search terms used in PubMed

1	Survey
2	Epidemiology
3	Epidemiological
4	Prevalence
5	#1 or #2 or #3 or #4
6	Pain [tiab]
7	Musculoskeletal [tiab]
8	“Chronic pain” [tiab]
9	Neck pain [tiab]
10	Back pain [tiab]
11	Shoulder pain [tiab]
12	Elbow pain [tiab]
13	Wrist pain [tiab]
14	Joint pain [tiab]
15	Hip pain [tiab]
16	Thigh pain [tiab]
17	Knee pain [tiab]
18	Leg pain [tiab]
19	Ankle pain [tiab]
20	Foot pain [tiab]
21	“Chronic non-cancer pain” [tiab]
22	“Non-cancer pain” [tiab]
23	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
24	Symptomatology [ti]
25	Co-morbidity [ti]
26	comorbidity [ti]
27	“Non-pain symptom” [ti]
28	#24 or #25 or #26 or #27
29	#5 AND #23 AND #28

Once the electronic searches were completed, the titles and abstracts were downloaded to EndNote X4. Duplicated references were removed from EndNote by using the “Find Duplicates” in the “References” command as well as sorting the publications by titles and authors’ surname in alphabetical order and visually comparing the publication titles. Lu, S. screened the titles and abstracts to identify studies that met the selection criteria. When there was confusion on whether or not to include references, Zheng, Z. was then consulted.

3.2.3 Data collection and extraction

Participant characteristics, research method, types of comorbidity, accompanying symptoms, ORs, epidemiological/percentage/association data were extracted. If studies were described as

a cohort study but only the baseline data were used, then such studies were considered to be cross sectional. This rule applied to demographic, comorbidity, and accompanying symptom data as well where only baseline data were used. The results were grouped according to International Classification of Disease into twelve categories [42], diseases of the nervous system (migraine, tension type headache, sleep disorders), diseases of the musculoskeletal system and connective tissue, mental and behavioural disorders, diseases of the digestive system, diseases of circulatory system, "endocrine, nutritional and metabolic diseases", diseases of the respiratory system, diseases of the genitourinary system, diseases of the eye and adnexa, disease of the ear and mastoid process, "symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (headache)" and other categories.

3.2.4 Methodological appraisal

The methodological rigour of the selected studies was assessed using NOS [41] which was recommended by the Cochrane Library [172]. NOS is a quality assessment tool that was designed for SRs of nonrandomised studies, such as case controlled and cohort studies [41]. This scoring system consists of eight items on the selection of participants, comparability of the groups, and exposure or outcome of the assessment, depending on whether the study was case controlled or cohort, of the study designs. Except for comparability of the groups where two scores may be given, other questions scored one, if the criteria were fulfilled, or none, if the criteria were not met. Content validity and inter-rater reliability of NOS have been established [41]. The quality of study was defined as very good if it scored eight or nine, good if it scored six to seven, satisfactory if it scored four to six, unsatisfactory if scored zero to three [173].

3.3 Results

3.3.1 Selection of studies

3.3.1.1 Search results and study selection

One thousand three hundred and ninety-three studies were found from databases searches (Table 3.2) and 798 studies were screened after duplication removed.

Table 3.2 Database search results

Database	Result
PubMed	378
CINAHL	52
PsycInfo	144
Cochrane Central	301
EBSCO	204
SCOPUS	314
Total	1393
Total after duplications removed	798

Of the 798 studies, 735 studies were excluded. The reasons for exclusion are presented in Table 3.3. Nine additional studies were obtained from hand searches of the included studies [174-182]. In total 72 studies were included [166-168,174-242]. The search procedure is illustrated in Figure 3.1.

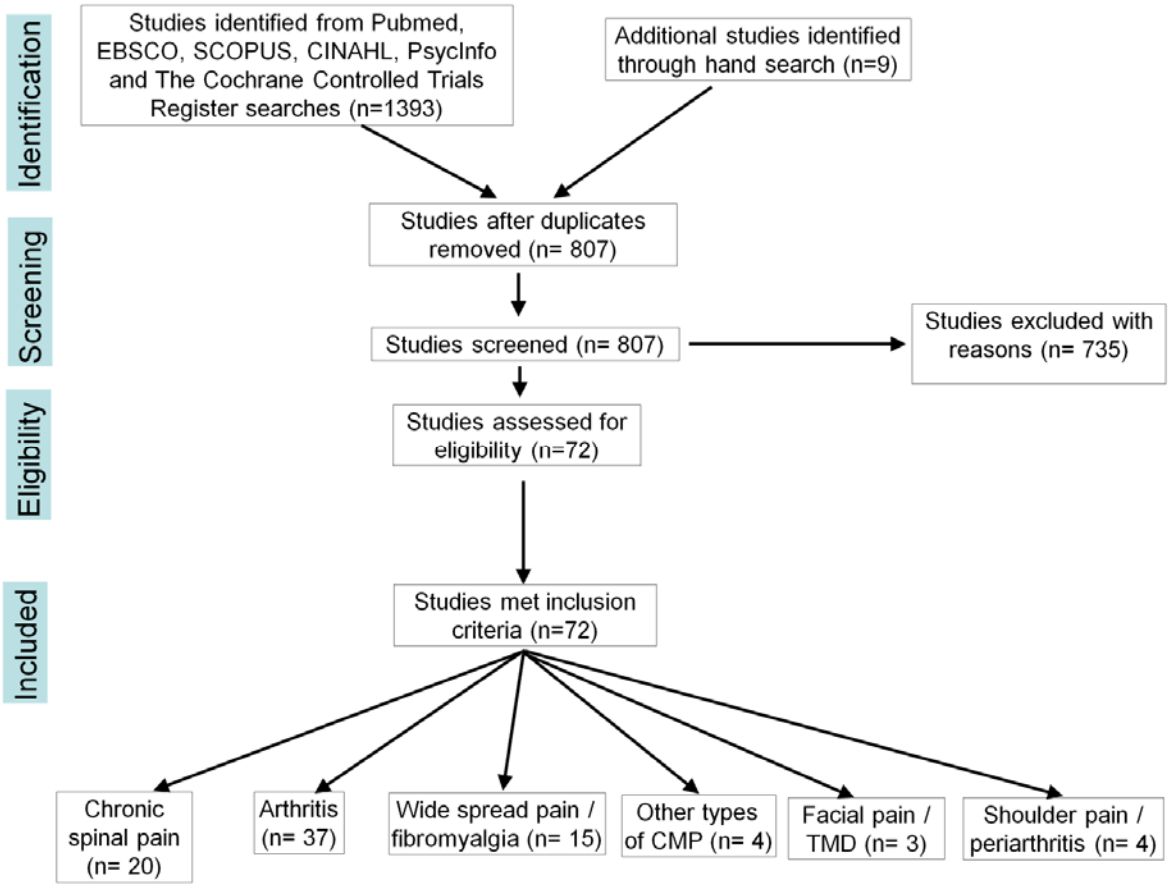


Figure 3.1 PRISMA diagram of the study inclusion procedures

The included studies had a range of 23 to 85,052 participants with a median of 590 and 635 and a total of 358,559 participants. Two studies reported the data from the same data set and were

only counted once in the total participants [176,202].

Table 3.3 Reasons for exclusion

Reasons for exclusion	Study
Non-musculoskeletal pain	153 studies [243-395]
No comorbidity/accompanying symptom/non-pain symptoms or no listed comorbidity/accompanying symptom	131 studies [396-526]
Non pain study	86 studies [527-612]
Review	62 studies [119,120,122,169,613-670]
No specific musculoskeletal pain (described as pain or bodily pain or the reporting of data is lumped together and unable to differentiate which part belongs to CMP)	55 studies [53,125,671-723]
CMP as comorbidity of other illnesses/symptoms	47 studies [724-770]
Non-CMP or uncertain of chronicity of musculoskeletal pain	45 studies [18,49,771-813]
Non-English/Chinese paper	42 studies [395,814-854]
Non-survey/interview study	18 studies [855-872]
Retrospective study	16 studies [873-888]
Cancer	15 studies [889-903]
Control group is not musculoskeletal pain free	15 studies [904-918]
Protocol only	11studies [919-929]
Correspondence letter or comment	9 studies [930-938]
Redundant	7 studies [939-945]
Book section	5 studies [946-950]
Outcome assessment study	4 studies [951-954]
No full data provided	3 studies [955-957]
Outcome assessment item is not musculoskeletal pain only	2 studies [958,959]
Erratum	2 studies [960,961]
Uncertain if participants have been counted more than once	1 study [962]
Cannot separate prospective and retrospective groups	1 study [963]
Book	1 study [964]
Comorbid depression was specifically chosen as part of inclusion criteria and made CMP all have depression	1 study [965]
Animal study	1 study [966]
Consensus	1 study [967]
Suspected duplication but EBSCO recorded this as new publication.	1 study [968]

The scores for the NOS are listed in Appendix 3 and Appendix 4. The summaries are listed in Table 3.4 and Table 3.5. For the case controlled studies, the average score was 2.18 for each study. The highest scored item was “Same method of ascertainment for cases and controls” whereas the lowest scored item was “Ascertainment of exposure”. For the cohort study, the average score was 2.75. The highest scored item was “Was follow-up long enough for outcomes to occur” and the lowest scored items were “Selection of the non exposed cohort”, “Demonstration that outcome of interest was not present at start of study”, " Assessment of

outcome", and "Adequacy of follow up of cohorts". Based on the criteria, only 14 studies were of satisfactory quality (Range: 4-5) [176,177,183,186,187,190,193,202,203,206,213,231,232,234] whereas the remaining studies were of unsatisfactory quality (Range: 0-3).

Table 3.4 NOS assessment summary of the included studies – case controlled studies (68 studies)

	Selection				Comparability	Exposure			
	Is the case definition adequate	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-Response rate**	**Total score**
Total score	16	25	11	23	24	6	34	9	148
Average	0.25	0.367647059	0.23913043	0.547619048	0.510638298	0.095238095	0.918918919	0.219512	2.18
Range	0-1	0-1	0-1	0-1	0-2	0-1	0-1	0-1	0-5

Table 3.5 NOS assessment summary of the included studies – cohort studies (4 studies)

	Selection				Comparability	Outcome			
	Representativeness of the exposed cohort	**Selection of the non exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design of analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**Total score**
Total score	3	0	3	0	1	0	4	0	11
Average	0.75	0	0.75	0	0.5	0	1	0	2.75
Range	0-1	0	0-1	0	0-1	0	1	0	2-3

3.3.2 Characteristics of selected studies

Comorbidities and accompanying symptoms of CMP

Of the 72 studies that reported comorbidities and accompanying symptoms of CMP, the countries where the studies were conducted are listed in Table 3.6. The majority of them came from USA.

Table 3.6 Country where the studies were taken

Country	Study
USA	31 studies [167,175-178,181,183,185,186,195,200-203,205,209-212,216,217,219,223,224,226-228,232,234,237,239]
Netherlands	5 studies [168,187,220,230,240]
Italy	4 studies [189,208,214,241]
Finland	3 studies [194,198,204]
Spain	3 studies [190,191,218]
Germany	3 studies [225,235,242]
Canada	5 studies [174,179,184,216,226]
Sweden	3 studies [180,197,199]
Norway	2 studies [196,213]
China	2 studies [166,229]
Turkey	1 study [188]
Possibly Turkey	1 study [182]
Not specified	1 study [215]
Columbia	1 study [231]
Online survey	1 study [221]
Slovenia	1 study [222]
Possibly Sweden	1 study [193]
Nigeria	1 study [192]
Possibly Netherlands	1 study [207]
International collaboration	1 study [206]
Australia	1 study [233]
France	1 study [236]
Lebanon	1 study [238]

The designs of the included studies are listed in Table 3.7. Majority of the studies were cross sectional studies.

Table 3.7 Design of the included studies

Design	Study
Cross sectional study	63 studies [166-168,174-178,181-183,185-200,202-209,211-214,216-226,229-235,237-242]
Cohort study	9 studies [179,180,184,201,210,215,227,228,236]

Types of study population

Of the included studies, chronic SP, arthritis, and fibromyalgia/widespread pain were studied the most. Detailed information about those conditions is presented in the relevant sections. The number and types of participants are presented in Table 3.8.

Table 3.8 Types of participants

Types of pain	Studies
Chronic SP	20 studies [167,168,175,177,178,186-188,190,192,193,197,206,208,209,229,231-233,240]
Arthritis	37 studies [166,176,177,179-181,185-187,190,194,200,202,206,207,210,212,213,217,219,220,222-224,227-232,234-240]
Fibromyalgia/Widespread pain	15 studies [182,184,188,189,196,197,201,203,204,214,216,218,225,226,241]
Other types of CMP	4 studies (3 non-specified CMP studies [174,191,199] and one study on chronic low back, hip, and knee pain [183])
Facial pain/temporal mandibular joint disorder	3 studies [195,215,242]
Shoulder pain/periarthritis	3 studies [198,205,211,221]

*some studies have been counted more than once due to the inclusion of other types of CMP.

Types of outcome measures

Within the included studies, various outcome measures were used and listed from Table 3.9 to Table 3.11. The most frequently used questionnaire for physical comorbidity was self-reported physical illness followed by author developed comorbidity/accompanying symptom list. For mental comorbidities, the most frequently used questionnaire was World Mental Health Survey initiative version of the WHO composite international diagnostic interview (CIDI) or CIDI-short form, followed by BDI. The most frequently reported assessment for both physical and mental comorbidities was self-report of pre-defined diagnosed chronic illnesses.

Table 3.9 Outcome measures of physical comorbidities/accompanying symptoms

Physical comorbidity assessment	Studies
Self-reported physical illnesses	8 studies [179,185,190,203,204,210,217,231]
Author made comorbidity/accompanying symptom list	7 studies [180,213,221,224,232,239,240]
A checklist of common physical disorders (name not given)	2 studies [187,192]
Body mass index	4 studies [181,207,223,238]
Deyo Charlson index for comorbidity	3 studies [227,228,237]
Self reported pain	1 study [219]
Medical evaluation	1 study [198]
Non-standardized questions/questionnaires (a checklist of common physical disorders)	1 study [187]
Common clinical characteristics of fibromyalgia syndrome such as non-restorative sleep, fatigue, tension-type headache, irritable bowel syndrome were also noted	1 study [188]
National health interview survey`	1 study [202]
Musculoskeletal outcomes data evaluation and management system	1 study [205]
Cumulative illness rating scale, cognitive screening test, Stroop color word test, Wechsler adult intelligence scale	1 study [207]
General health survey for comorbidities	1 study [211]
Mattis Dementia Rating Scale	1 study [212]
Clinical and verbal questionnaire in relation to cranio-cervico-facial pain and otic symptomatology.	1 study [215]
Fibromyalgia 18 tender spots	1 study [218]
Number of painful joint sites.	1 study [220]
Medical Outcomes Study sleep scale for sleep disturbances	1 study [225]
PainDETECT questionnaire for sensory symptoms	1 study [225]
The Pittsburgh Sleep Quality Index	1 study [229]
Comorbidity is assessed with a self-reported health module of the Central Bureau of Statistics in the Netherlands which encompasses 24 chronic diseases	1 study [230]
Functional comorbidity index	1 study [236]
Index of Sexual Satisfaction	1 study [241]

Table 3.10 Outcome measures of mental comorbidities/accompanying symptoms

Mental comorbidity assessment	Studies
World mental health survey initiative version of the WHO CIDI or CIDI-short form	10 studies [166,176,177,186,187,192,202,206,224,232]
BDI	4 studies [174,175,188,216]
Self-reported mental/psychiatric illnesses	4 studies [189,203,210,231]
Center for epidemiological studies-depression scale	2 studies [185,219]
Symptom checklist 90 or the revised version	2 studies [184,199]
Diagnostic interview schedule-version III-A, Hamilton rating scale for depression	2 studies [175,214]
Zung depression scale	2 studies [193,222]
Hospital Anxiety and Depression Scale	2 studies [196,220]
Structured Clinical Interview for DSM-IV Axis I Disorders	2 studies [182,241]
Structured clinical interview for DSM-III-R	1 study [178]
Anxiety sensitivity index	1 study [174]
Marks and Mathews fear questionnaire, panic attack questionnaire, structured clinical interview for DSM-IV	1 study [174]
Self-reported suicide plan or attempt	1 study [186]
Primary care evaluation of mental disorders	1 study [191]
Zung's self rating anxiety scale	1 study [222]
Comprehensive psychopathological rating scale for self administration, Montgomery–Åsberg depression rating scale, structured clinical interview for diagnosis questionnaire, depression rating self-report questionnaire, employment/insurance-benefit status, periods of sick leave and/or partial (temporary or permanent) disability pension	1 study [197]
Present state examination (mental disorder diagnoses)	1 study [198]
Temperament character inventory	1 study [199]
Neurological and psychiatrical assessment	1 study [208]
PTSD checklist	1 study [201]
Depression subscale of symptom checklist 25	1 study [204]
Geriatric Depression Scale.	1 study [212]
Kessler 10-item scale score (to screen populations for nonspecific psychological distress in the anxiety–depression spectrum and serious mental illness)	1 study [231]
Fear-Avoidance Beliefs Questionnaire physical activity subscale, modified for the knee)	1 study [219]
Beck Anxiety Index	1 study [219]
Tampa Scale for Kinesiophobia	1 study [220]
The Borderline Personality Disorder scale from the International Personality Disorder Examination Screening Questionnaire	1 study [224]
Hazan and Shaver's (1987) attachment style (measures secure, avoidant, and anxious attachments)	1 study [232]
PHQ for depressive, panic, and anxiety disorders	1 study [225]
Adult Self-Report (anxiety and depression scales)	1 study [240]
Major Depression Inventory	1 study [242]

BDI: Beck depression inventory
CIDI: composite international diagnostic interview
PHQ: Patient Health Questionnaire
PTSD: Post traumatic stress disorder

Table 3.11 Outcome measures of both physical and mental comorbidities/accompanying symptoms

Both physical and mental comorbidity assessment	Studies
Self report of pre-defined diagnosed chronic illnesses	2 studies [190,235]
Patient questionnaire	1 study [219]
Interview and medical exam	1 study [212]
Medical/psychiatric evaluation	1 study [195]
National health interview survey`	1 study [202]
Symptom checklist 25	1 study [204]
Uncertain of questionnaire, author only mentioned comorbid diseases and psychiatric history were recorded. Mattis Dementia Rating Scale, and Geriatric Depression Scale.	1 study [212]
The questionnaire was designed by the panel which consisted of eight domains: 1) demographics, 2) physical and mental health status, 3) health insurance, 4) health care utilization and access to health care, 5) medical home, 6) family functioning, 7) parents' health, and 8) neighbourhood characteristics.	1 study [234]
Record from Survey of Disability, Ageing and Carers	1 study [233]
The checklist for fibromyalgia is adapted from the Memorial Symptom Assessment Scale (MSAS)	1 study [226]
Comorbidity is assessed with a self-reported health module of the Central Bureau of Statistics in the Netherlands which encompasses 24 chronic diseases	1 study [230]

3.3.2.1 Methods of data collection

The methods of data collection are listed in Table 3.12. The majority of studies (86%) used interview/survey (33%), questionnaire (33%), or a combination of them (19%). Five clinical trials did not report the method used for collecting data.

Table 3.12 Method of data collection

Method of data collection	Study
Interview or survey	24 studies [166,167,175,176,182,183,185-187,192,195,201,203,208,210,213,217,224,227,228,232-234]
Questionnaire	24 studies [168,180,181,184,193,194,196,199,204,205,209,214,221,222,225,226,229,230,236,237,239-242]
Both interview/survey and questionnaire	14 studies [174,177-179,189-191,197,198,202,206,220,231,238]
Clinical trial, only mentioned comorbid diseases will be recorded	5 studies [200,212,215,216,218]
Physical examination, questionnaire, and interview/survey	4 studies [207,219,223,235]
Physical examination and questionnaire	2 studies [188,211]

3.3.2.2 Summary of types of participants

The types of participants are listed in Table 3.13. The majority of the studies recruited from the general public (31%) followed by arthritis/rheumatology clinic patients (22%) and fibromyalgia participants (13%).

Table 3.13 CMP studies and their participants

Participant	Studies
General population	22 studies [166,167,176,177,185-187,190-192,198,202,204,206,213,224,231,232,234,238-240]
Arthritis/rheumatology clinic patients	16 studies [179,180,194,200,207,210,212,219,220,223,227,228,230,235-237]
Fibromyalgia	9 studies [184,189,196,214,216,218,225,226,241]
Chronic LBP	6 studies [175,178,183,188,193,233]
Shoulder pain (rotator cuff tear, capsulitis)	3 studies [205,211,221]
Various physical illness groups	2 studies [208,209]
Labourer	1 study [168]
Attending treatment programme	1 studies [174]
Facial pain	1 study [195]
Non-specific musculoskeletal pain	1 study [199]
Sickness absentees	1 study [197]
Twins	1 study [203]
Adult women	1 study [201]
Otolaryngologic clinic patient	1 study [215]
Children with one or no chronic illnesses	1 study [217]
Patients who visit GP	1 study [222]
High school student	1 study [229]

Dental clinic	1 study [242]
Medicare beneficiaries	1 study [181]
Did not describe	1 study [182]

GP: General practitioner
LBP: Low back pain

As there were many studies that reported different types of pain, the data of the top three main pain groups were listed and described in the following sections. They were chronic SP, arthritis, and widespread pain/fibromyalgia. The summary of the comorbidities and accompanying symptoms are listed from Table 3.46 to Table 3.48 (p. 126).

For the following section, several studies were included in two or all of the three major CMP types; and overlaps are specified in the footnotes of Table 3.14, Table 3.26, and Table 3.39. The characteristics of the included studies were presented in the table at the beginning of each section to avoid data duplication.

3.3.3 Chronic spinal pain and its comorbidities

Nineteen studies provided data for chronic SP. One study only provided p value for the association without any OR or percentage data [240]. This study was included but not described in the following comorbidity and accompanying symptom categories. The comorbidities and accompanying symptoms can be categorised into diseases/accompanying symptoms of

- the mental and behavioural disorders,
- nervous system,
- musculoskeletal system and connective tissue,
- digestive system,
- circulatory system,
- “endocrine, nutritional and metabolic diseases/symptoms”,
- respiratory system,
- other kinds of pain,
- genitourinary system,
- eye and adnexa system,

- ear and mastoid process system,
- symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, and
- others.

The majority of the included studies reported findings of comorbid mental and behavioural disorders (13 studies), whereas fewer studies reported findings in accompanying "Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified" (three studies).

The main comorbidities/accompanying symptoms for chronic SP included headache, arthritis, depression, GAD, panic disorder, mood disorder, alcohol use disorder, digestive ulcer, heart disease, hypertension, other lung disease (apart from tuberculosis, and asthma), migraine, and chronic pain.

The characteristics of the included 20 chronic SP studies are presented in Table 3.14. Except for one study which included school children [229], and another survey which included the general public from 15 years old and over [229], all studies included adult participants. Eight studies recruited participants from the general public [167,177,186,187,190,192,206,232] and seven studies specially recruited chronic SP participants [175,178,188,193,208,209,233]. Seven studies identified chronic SP by using patient completed surveys [167,177,186,187,192,206,232], five studies identified chronic SP by using a pre-defined criteria [175,178,188,193,208]. Seven studies were carried out in USA [167,175,177,178,186,209,232], one was an international collaboration [206], whereas the rest were from 11 other countries.

Table 3.14 Characteristics of included 20 chronic SP studies

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
Atkinson et al. [175]	n=146, 97 chronic LBP from medical centre and 49 healthy controls recruited from Veteran Administration volunteers, advertisements and service organization in San Diego.	Pre-defined criteria requiring the presence of chronic SP.	USA.	Patient: 46.7 years (range 23-64) Healthy control who did not have LBP for more than one week: 45.5 years (range 22-65)
Braden et al. [186]	n=5689, G (27.9% arthritis, 33.5% chronic	Patient's response to a	USA	With lifetime self-reported pain:

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
	back/neck problems)	survey checklist of arthritis/ rheumatism, chronic back or neck problems		18-44 years: 42.7% 45-64 years: 36.1% 65 years and older: 21.2% Without lifetime self-reported pain: 18-44 years: 63.3% 45-64 years: 25.0% 65 years and older: 11.4%
Buist-Bouwman et al. [187]	n=7076, G (9% chronic back trouble, 8.3% rheumatism)	Survey question asking presence of chronic back trouble or rheumatism	Netherland	Not described
Cakit et al., [188]	n=123, 93 cervical myofascial pain females, 30 female healthy cervical pain free control.	Participants fulfilling myofascial pain syndrome criteria including cervical myofascial pain syndrome lasting for more than 3 months and with active trigger point in neck and upper back regions.	Turkey	Cervical myofascial pain group: 33.69± 6.25 years (range, 18–53) Healthy control: 31.44±8.24 years (range, 22-45)
Dominick et al. [231]	n=12488, G (24.2% neck and back disorder, 14.4% arthritis, 2.9% osteoporosis)	Survey question asking presence of chronic pain and site of pain	New Zealand	15 years and over. Mean and SD not stated.
Fernandez-de-Las-Penas et al. [190]	n=29478, G (7616 arthritis (25.8%), 6654 cervical pain (22.6%), 6793 LBP (23%), 1945 osteoporosis (6.6%))	Uncertain, authors only mentioned analysing presence of chronic diseases/symptoms	Spain	16-30 years: 4536 31-50 years: 11170 51-70 years: 8198 >70 years: 5574

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
Gureje et al. [192]	n=6752, G (16.4% chronic SP)	Survey question asking presence of chronic SP	Nigeria	18-29 years: 904 30-44 years: 676 45-59 years: 356 60+ years: 209
Hägg et al. [193]	n=572, chronic LBP referred to orthopaedic department	Pre-defined criteria requiring the presence of chronic SP.	Does not mention, but the project is titled Swedish Spine Study.	Chronic LBP: 43±8.3 years General population with back pain (as collected by Central Statistical Bureau of Sweden, of which 55% is Chronic LBP: 46±8.5 years General population free of back pain: 44±9.5 years
Ijzelenberg & Burdorf, 2004 [168]	n=505, L (36(7%) had chronic LBP	Survey question asking presence of chronic LBP	Netherlands	41.5± 9.8
Lachlan A. McWilliams & Bailey et al. [232]	n=5645, G (27.1% arthritis, 29.2% chronic back/neck problem	Survey question asking presence of chronic back/neck problems or and arthritis	USA	Not described
McWilliam et al. 2004 [177]	n=3032, G (19.4% arthritis, 20.3% back pain	Survey question asking presence of back pain and arthritis	USA	Not stated
Polatin et al. [178]	n=200, chronic LBP patients entering a functional restoration programme	Pre-defined criteria requiring the presence of chronic SP.	USA	Not stated
Schofield et al. [233]	n=8864, general public with chronic LBP	Health records	Australia	45-64 years old
Siu et al. [229]	n=1518, H (173 have chronic pain only, and 290 have chronic pain	Uncertain, method of CMP	SAR, China	11-13 years: 34.7% 14-16 years: 49.1% 17-19 years: 16.2%

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
	comorbid with sleep disturbances. Of chronic pain only, 9.1% have chronic LBP, 9.1% have chronic upper back pain. Of chronic pain comorbid with sleep disturbances, 17.2% are chronic LBP, 10.9% are chronic upper back pain.	identification not described in the publication		
Tsang et al. [206]	n=85052, G (20% chronic SP, 16.5% arthritis)	Survey question asking presence of chronic back/neck problems, arthritis, and rheumatism	IntS	Overall: 42.9 years Developing countries: 38.2 years Developed countries: 45.5 years
Verri et al. [208]	n=35, chronic LBP, source not described as the chronic LBP group is a control group	Pre-defined criteria requiring the presence of chronic SP.	Italy	Chronic LBP: 44 years (range 20-72)
Von Korff et al. [167]	n=5692, G (Chronic SP lifetime prevalence 29.3%, 12 months prevalence 19.0%)	Patient's response to a checklist of chronic SP.	USA	18-29 years: 24.1% 30-44 years: 32.1% 45-59 years: 26.7% 60+ years: 17.1%
Whitson et al. [209]	n=211, vertebral fracture,	Vertebral fractures according to radiograph	USA.	Vertebral fracture cohort: 80.8±5.5 years
Linder, Ekholm, Jansen, Lundh, & Ekholm, 2009 [197]	n=630 long term sick leavers (119 (19%) were SP)	Diagnosed by psychiatry, orthopaedic surgery and rehabilitation medicine specialists	Sweden	45.6 ±8.5 years
Ligthart et al.[240]	n=11948, twins and relatives of twins. Participants must have participated in the previous survey in order to be in the current survey (9.1% had chronic back pain and	Survey question asking the location and frequency of pain.	Netherlands	All participants: 44.5±15.7 years No pain group: 43.4±16.3 years Occasional pain group: 44.3±15.4 years Frequent pain group:

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
	6.4% had chronic neck pain			45.7±16.2 years

SAR: Special administrative region
LBP: Low back pain
SP: Spinal pain
G: General population
H: High school student
L: Labourer
IntS: International study including Colombia, Mexico, USA, Belgium, France, Germany, Italy, Netherlands, Spain, Ukraine, Israel, Lebanon, Nigeria, South Africa, Japan, PRC (Beijing and Shanghai),and New Zealand.
USA: United State of America
Six studies also provided data for arthritis and were also included in the arthritis section [186,187,190,206,229,231]

Two studies also provided data for fibromyalgia and were also included in the fibromyalgia section [188,197]

3.3.3.1 Mental and behavioural disorders as comorbidities or accompanying symptoms of chronic SP

Thirteen studies provided findings on mental and behavioural disorders as comorbidity or accompanying symptom of chronic SP [167,175,177,178,186,187,192,193,197,206,208,209,233]. Their findings are summarized in the following paragraphs and presented from Table 3.15 to Table 3.16.

Percentage data of mental and behavioural disorders as comorbidity or accompanying symptoms of chronic SP

The percentage data summary of comorbid mental and behavioural disorders is listed in Table 3.15. The percentage data of all the comorbid mental and behavioural disorders among the sampled population ranged from 0% to 97%.

Of all the comorbid mental conditions, any kind of anxiety affected most of the chronic SP (minimally 21.6%) and bipolar I or II was least likely to occur in chronic SP (maximally 4.4%) amongst all the reported comorbid mental conditions. Except for axis II personality disorders and non-specified mental conditions, all other reported specific mental conditions were reported by at least two studies.

Table 3.15 Summary of occurrence of mental and behavioural disorders as comorbidities or accompanying symptoms of chronic SP

Mental conditions	Study	Range of percentage
Somatoform disorder	[178,208]	1% and 97%
At least one psychiatric disorder (other than tobacco use disorder)	[175]	81.4%
GAD	[167,175,178,208]	2% to 65.7%
Alcohol related disorders	[167,175]	2.1% and 64.9%
Major depression/depression	[167,175,178,193,197,208,209,233]	11.4% to 64%
All/any kinds of anxiety disorder	[167,175,178,209]	21.6% to 45.7%
Recent episode of psychiatric disorder	[175]	41.2% (reported by one study only)
Abuse or dependence of substance	[167,175,178]	4.1% to 36%. One study showed non association between chronic SP and drug abuse/dependence.
Phobias (including simple phobia, social phobia, and Specific phobia)	[167,178,208]	0% to 25.7%
Dysthymia	[167,175,178,208]	2% to 23.7%
Any mood disorder	[167]	17.5% (reported by one study only)
Obsessive compulsive disorder	[175,178,208]	0% to 13.4%
Panic disorder	[167,175,178,208]	2.8% to 8.2%
PTSD	[167,178]	1% and 7.3%
Bipolar I or II	[167,178]	2% and 4.4%

GAD: Generalized anxiety disorder
PTSD: Post traumatic stress disorder

Odds ratios of mental and behavioural disorders as comorbidity or accompanying symptoms of chronic SP

The OR summary of mental and behavioural disorders as comorbidities or accompanying symptoms of chronic SP are summarised in Table 3.16. The OR ranged from 1.4 to 6.2. Comorbid suicide ideation occurred 1.4 times more and comorbid major depressive/depression occurred 6.2 times more amongst chronic SP than patients without chronic SP (the studies did not provide data for whether the control group had other kinds of pain. The control groups were general public without chronic SP). On the minimum scale, patients with chronic SP were 2.54 times more likely to have GAD than patients without chronic SP; and on the maximum scale, those with chronic SP were at least 1.6 times more likely to have had suicidal ideation, suicide plan, and suicide attempt. There were conflicting findings in “all anxiety

disorders", "abuse or dependence on other substances", and phobia as comorbidities of chronic SP amongst the reports.

Dysthymic disorder, PTSD, bipolar, secure/avoidant/anxious attachments, suicide ideation, suicide plan, and suicide attempt were studied by only one study.

Table 3.16 Summary of OR ranges of mental and behavioural disorders as comorbidity or accompanying symptoms of chronic SP

Mental conditions	Study	Comparison group	Odds ratio
Major depression	[167,177,193,206]	General public without SP	2.5 to 6.2
Abuse or dependence on other substances	[167,187,192]	General public without SP	1.3 to 3.2. One study reported no association between CMP and drug abuse/dependence
Dysthymic disorder	[167]	General public without SP	3.2 (reported by one study only)
GAD	[167,177]	General public without SP	2.54 and 2.6
Panic disorder	[167,177]	General public without SP	2.0 and 2.69
PTSD	[167]	General public without SP	2.6 (reported by one study only)
Mood disorder	[167,187,192]	General public without SP	1.7 to 2.5
All anxiety disorders	[167,187,192,206]	General public without SP	1.5 to 2.3. There was one study reported no increased chance associated with CMP.
Other – any mental disorder	[167]	General public without SP	2.3 (reported by one study only)
Phobia	[167]	General public without SP	1.7 to 2.1. One study reported no association between CMP and agoraphobia without panic. (Findings on phobia were reported by one study only)
Alcohol use disorder	[167]	General public without SP	1.6 to 2.0 (reported by one study only)
Bipolar	[167]	General public without SP	2.0 (reported by one study only)
Suicidal ideation, suicide plan, and suicide attempt	[186]	General public without SP	1.4 to 1.6 (reported by one study only)

GAD: Generalized anxiety disorder
GP: General practitioner
PTSD: Post traumatic stress disorder
SP: Spinal pain

3.3.3.2 Diseases/symptom of the nervous system as comorbidities or accompanying symptoms of chronic SP

Six studies reported findings in neurological disorders [167,188,190,209,229,233] (Table 3.17). Different conditions were studied in the five studies. The most common comorbidity was migraine. The percentage of accompanying migraine ranged from 12.5% to 25.39%. The percentages of neurological disorders ranged from 1.4% to 54%. Sleeping problems (insomnia, narcolepsy, non-restorative sleep, and disturbed sleep) ranged from 12.8% to 76%. Having chronic SP increased the odds of having epilepsy by 1.7 times [167] and migraine by 1.33-5.2 times.

Table 3.17 Neurological disorders comorbidities and accompanying symptom of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Whitson et al. [209]	Memory loss: 54% Feeling tired much of the time: 49.8% Balance problems: 49.8% Muscle weakness: 45.5% Difficulty sleeping at night: 38.4% Numbness or tingling anywhere: 30.3% Confused thinking: 23.2% Shakiness or trembling: 17.5% Sleep problems (insomnia, narcolepsy): 12.8% Parkinson's disease: 1.4%	
Siu et al. [229]	Percentage of sleep disturbance amongst teenagers with a particular type of chronic pain are listed below: Low back(n=66): 76.0% Upper back (n=47): 66.8% Neck (n=91): 71.0%	
Schofield et al. [233]	Diseases of the nervous system: 8.7%	No data
Von Korff et al. [167]	Epilepsy: 3.0% (SE:0.5) Migraine: 12.5% (SE: 0.9)	Compared with general public without chronic SP: Epilepsy: 1.7 (1.1-2.7) Migraine: 5.2 (4.1-6.4)
Fernandez-de-Las-Penas et al. [190]	Migraine within chronic cervical pain: 25.39% Migraine within chronic LBP: 21.43%	Compared with general public without chronic SP: The adjusted ORs for diseases independently significantly associated with a higher likelihood of suffering

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
		Migraine (within chronic neck pain): 2.31 (1.98–2.68) Migraine (within chronic Low back pain): 1.33 (1.14-1.55)
Cakit et al., [188]	Non-restorative sleep: 68.8% Fatigue: 36.6% Tension type headache: 43%	No data

CI: Confidence interval
LBP: Low back pain
OR: Odds ratio
SE: Standard error
SP: Spinal pain

3.3.3.3 Diseases of the musculoskeletal system and connective tissue as comorbidities or accompanying symptoms of chronic SP

Six studies provided findings on CMP as comorbidities or accompanying symptom of chronic SP [167,168,188,192,209,233] (Table 3.18). The percentage of arthritis ranged from 1.5% to 71%, whereas other types of musculoskeletal pain ranged from 5.9% to 64.9%. Having chronic SP increased the odds of having arthritis by 3.0 – 7.9 times and other types of musculoskeletal pain by 2.62 to 7.12 times. The publications did not make a clear differentiation between chronic SP and arthritis. The comorbid arthritis may well overlap with spinal joint regions.

Table 3.18 Musculoskeletal pain as comorbidity of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Gureje et al. [192]	No data	Compared to general public without chronic SP: Arthritis: 7.9 (5.5-11.3)
Ijzelenberg et al. [168]		Compared to hard labour workers without LBP: Chronic neck pain: 4.81 (1.48-15.57), *Chronic shoulder pain: 2.62 (0.89-7.73)* Chronic complains of elbow-wrist-hand pain: 7.12 (1.48-34.39) Chronic upper extremity

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
		complaint: 3.59 (1.47-8.80)
Von Korff et al. [167]	Arthritis: 51.0 (1.5%)	Compared with general public without chronic SP: Arthritis: 3.0 (3.2-4.7)
Whitson et al. [209]	Symptoms in previous month: Pain (64.9%) Muscle cramps: 44.6% Arthritis: 71% Osteoporosis: 61% Broken bone(s): 61.1% Chronic pain syndrome: 6.6%	No data
Schofield et al. [233]	Prevalence of comorbidity: Arthritis: 21.7% Other diseases of the musculoskeletal system: 5.9%	
Cakit et al. [188]	Fibromyalgia: 23.6%	

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OR: Odds ratio

3.3.3.4 Diseases/symptom of the digestive system as comorbidities or accompanying symptoms of chronic SP

Five studies reported digestive disorders as chronic SP comorbidities [167,188,192,209,233]. Their findings are listed in Table 3.19. Accompanying Irritable bowel syndrome percentage ranged from 1.9% to 30.1%. Apart from irritable bowel syndrome, the most common comorbidity/accompanying symptom was nausea (13.7%), and the comorbidity with the highest OR was ulcer in the digestive system (4.0). Except for irritable bowel syndrome, each accompanying symptom/comorbidity was only investigated by one study.

Table 3.19 Digestive comorbidity as accompanying symptom of chronic SP

Studies	Percentage of comorbidity accompanying symptoms	OR and 95% CI
Gureje et al. [192]	No data	Compared with general public without chronic SP: Peptic ulcer: 3.1 (1.6-6.0)
Von Korff et al. [167]	Irritable bowel syndrome: 1.9% (SE:0.4) Ulcer: 6.6% (SE:0.8)	Compared with general public without chronic SP: Irritable bowel syndrome: 2.4 (1.1-5.3) Ulcer: 4.0 (2.6-5.9)
Whitson et al. [209]	Nausea: 13.7%	No data
Schofield et al. [233]	Diseases of the digestive system: 3.4%	
Cakit et al. [188]	Irritable bowel syndrome: 30.1%	

CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.3.5 Diseases/symptoms of the circulatory system as comorbidities or accompanying symptoms of chronic SP

Four studies reported data on circulatory system related comorbidities/accompanying symptoms with their results listed in Table 3.20 [167,192,209,233]. Three studies provided percentage data and two provided OR for circulatory system related conditions. Stroke, heart diseases, and high blood pressure ranged from 4.3% - 26.6% respectively. Other comorbidities/accompanying symptoms were investigated by single studies and ranged from 4.0% for heart attack to 53.6% for shortness of breath with exertion. Two studies found chronic SP was not associated with heart attack.

Having chronic SP was associated with a 1.5-2.9 times greater likelihood of having high blood pressure. There was a conflict finding in the association between heart attack, stroke and chronic SP.

Table 3.20 Circulatory system related comorbidities and accompanying symptoms of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Gureje et al. [192]	No data	Compared with general public without chronic SP: Heart disease: 11.4 (2.2-58.7) High blood pressure: 2.9 (1.5-5.8). *Stroke: 1.7 (0.4–6.9)* *Heart attack: 2.7 (0.6–12.0)*
Von Korff et al. [167]	Stroke: 4.3% (SE:0.5), High blood pressure: 26.6% (SE:2.0) Heart disease: 6.9% (SE:0.8), Heart attack: 4.0% (SE:0.6),	Compared with general public without chronic SP: Stroke: 1.5 (1.1-2.1) High blood pressure: 1.5 (1.2-2.0) *Heart disease: 1.3 (1.0-1.7)* *Heart attack: 0.9 (0.6-1.4)*
Whitson et al. [209]	Chest pain or pressure with exertion:10.9% Shortness of breath at rest:10.4% Shortness of breath with exertion 53.6% Angina pectoris:11.4% Congestive heart failure:4.7% Heart attack:5.7% Stroke:6.7%	No data
Schofield et al. [233]	Heart disease: 3.6% Hypertension: 19.3%, Other diseases of the circulatory system (other than Heart disease and hypertension): 4.9%	

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.3.6 Endocrine, nutritional and metabolic diseases/symptoms as comorbidities or accompanying symptoms of chronic SP

Four studies reported findings on endocrine conditions [167,192,209,233], including diabetes, thyroid disease, and high cholesterol (Table 3.21). All four reported findings on diabetes with two finding no associations between chronic SP and diabetes [167,192] and three reporting that the percentages of diabetes ranged from 0.5% to 8.2% [167,209,233]. Thyroid disease was reported by one study as not associated with chronic SP [192]. High cholesterol was reported to occur in 6.8% of chronic SP [233].

Table 3.21 Endocrine, nutritional and metabolic diseases/symptoms as comorbidity or accompanying symptoms of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Gureje et al. [192]	No data	Compared with general public without chronic SP: *Diabetes: 0.8 (0.1-4.0)* *Thyroid disease: 0.4 (0.08–2.6)*
Von Korff et al. [167]	Diabetes: 8.2% (SE:1.0)	Compared with general public without chronic SP: *Diabetes: 1.2 (0.8-1.7)*
Whitson et al. [209]	Diabetes mellitus: 0.5%	
Schofield et al. [233]	Other endocrine/nutritional and metabolic disorders: 3.0% Diabetes: 6.8% High cholesterol: 6.8%	No data

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.3.7 Diseases/symptoms of the respiratory system as comorbidities or accompanying symptoms of chronic SP

Four studies reported findings of respiratory conditions (Table 3.22) [167,192,209,233]. The percentage of asthma ranged from 7.2% to 16.9%. And the OR for lung diseases, apart from asthma and tuberculosis, ranged from 1.7 to 2.9. There was a conflicting finding for asthma where one study [167] found an association but the other study [192] found chronic SP did not increase the chance of having asthma. The finding for tuberculosis was either no association or no data available.

Table 3.22 Respiratory comorbidities and accompanying symptom of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Gureje et al. [192]	No data	Compared with general public without chronic SP: Other lung disease (lung diseases apart from asthma, and tuberculosis): 2.9 (1.1-7.4) *Asthma: 1.2 (0.2–6.9)* *Tuberculosis: 7.1 (0.6–82.2)*

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Von Korff et al. [167]	Asthma: 16.9% (SE:1.3) Tuberculosis: 0.1% (SE:0.1) Other lung disease: 4.1% (SE:0.8)	Compared with general public without chronic SP: Asthma: 1.8 (1.4-2.1) Tuberculosis: no data, *Other lung disease (lung diseases apart from asthma, and tuberculosis): 1.7 (1.0-2.7)*
Whitson et al. [209]	Symptoms in previous month: lung disease: 15.2%	No data
Schofield et al. [233]	Asthma: 7.2% Diseases of the respiratory system: 3.3%	

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.3.8 Other kinds of pain

Four studies reported findings on other kinds of pain [167,186,192,231] (Table 3.23). Percentage of chronic pain ranged from 18.9% to 68.6% within chronic SP [167,231]. Chronic SP was 3.4 to 4.8 times more likely to have one other chronic pain and up to 9.1 times more likely to have any other pain.

Table 3.23 Other kinds of pain conditions as comorbidities and accompanying symptom of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Braden et al. [186]	More than one lifetime pain condition: 39.1%	No data
Gureje et al. [192]	The prevalence of chronic SP amongst respondents with at least one other chronic pain condition (54.2% SE:2.6) is approximately three times higher than among those with no other chronic pain (14.8% SE:1.0).	Compared with general public without chronic SP: Other pain (chest pains, joint pains, frequent headaches): 4.5 (2.6-7.5) Any pain (persistent pain in any other body parts): 9.1 (6.3-13.1)
Von Korff et al. [167]	Other chronic pain: 18.9% (SE:1.4) Any chronic pain: 68.6% (SE:1.5)	Compared with general public without chronic SP: Other chronic pain (other than chronic SP, arthritis, or headache): 3.7 (2.9-4.7)

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
		Any chronic pain: 4.8 (3.9-5.8)
Dominick et al. [231]	Percentage of chronic pain within CMP: Chronic neck/back disorder: 36.8%	Compared with general public without chronic SP: The OR for chronic pain after adjusted for sociodemographic variables and the physical and mental conditions: Chronic neck/back disorder: 3.4 (95% CI 2.9-3.9) Chronic pain is defined as pain lasted more than six months and may be in any parts of the body ranging from head to toes and including chest, stomach, and pelvic pain.

CI: Confidence interval
CMP: Chronic musculoskeletal pain
OR: Odds ratio
SE: Standard error

3.3.3.9 Diseases/symptoms of the eye and adnexa and disease/symptoms of the ear and mastoid process as comorbidities or accompanying symptoms of CMP

Three studies reported findings for eye and adnexa diseases/symptoms [167,209,233] and two studies reported findings for ear and mastoid process conditions (Table 3.24) [167,209]. Percentage of comorbidities/accompanying symptoms in the eye diseases category ranged from 1.7% to 74.9%. All of the specific eye diseases were reported by a single study. The comorbidity with the highest percentage was cataract. Vision impairment was 2.6 times more likely to occur in chronic SP.

The percentage of ear and mastoid process diseases/symptoms amongst chronic SP was between 6%-8.3%. Hearing impairment was consistently reported at approximately 6% by both studies [167,209]. Hearing impairment was not significantly associated with chronic SP (OR:1.5, 95% CI 1.0-2.2) [167].

Table 3.24 “Eye and adnexa” and “ear and mastoid process” conditions as comorbidities and accompanying symptom of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Eye and adnexa diseases/symptoms		
Von Korff et al. [167]	Vision impairment: 7.1% (SE:0.8)	Compared with general public without chronic SP: Vision impairment: 2.6 (1.8-3.9)
Whitson et al. [209]	Symptoms in previous month: problems with eyesight: 43.1% glaucoma: 15.2% cataract: 74.9%	
Schofield et al. [233]	Diseases of the eye and adnexa: 1.7%	No data
Ear and mastoid process diseases/symptoms		
Von Korff et al. [167]	Hearing impaired: 6.0% (SE:0.7)	Compared with general public without chronic SP: *Hearing impaired: 1.5 (1.0-2.2)*
Schofield et al. [233]	Deafness/hearing loss: 6.6% Diseases of the ear and mastoid process: 8.3%	No data

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.3.10 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified as accompanying symptoms of chronic SP

Two studies reported findings on headache as an accompanying symptom of chronic SP [167,192]. The prevalence within the sample ranged from 14.6-31.9% (Table 3.25). Having chronic SP increased the odds of having headache by 4-7 times.

Table 3.25 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified as accompanying symptoms of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Von Korff et al. [167]	Other headache: 14.6% (SE: 1.4)	Compared with general public without chronic SP: Other headache: 4.0 (2.9-5.3)
Gureje et al. [192]	Headache: 31.9% (SE:2.2)	Compared with general public without chronic SP: Headache: 7.0 (4.9-10.1)

CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.3.11 Diseases/symptoms of the remaining disease systems as comorbidities or accompanying symptoms or other findings of chronic SP

Three studies reported findings for the genitourinary system category (Appendix 10) [193,209,233]. One reported 35.6% of chronic SP had incontinence [209] whereas the other study found the percentage for diseases of genitourinary system was 2% [233]. Another study (n=572) included 294 chronic LBP participants and 278 age and gender matched general population [193]. The study found the chronic LBP population more likely to report back pain during pregnancy (OR=2.3, 95% CI 1.1-4.5), back pain during menstruation (OR=2.7, 95% CI 1.5-5.1), and an increased number of deliveries (OR=1.6, 95% CI 1.1-2.1) in comparison with general population without back pain.

Four studies reported individual data for other comorbidities/accompanying symptoms [167,193,209,233] (Appendix 11). The percentage of other comorbidity/accompanying symptoms ranged from 0.3% to 87.1%. HIV and neoplasms were both 0.3% with chronic SP and "all mental, pain or physical disorder" was 87.1% within chronic SP. Von Korff et al. reported cancer was not associated with chronic SP. Chronic SP was five times more likely to be accompanied with HIV and 2.3 times more likely to be associated with smoking comparaed to those without chronic SP.

3.3.4 Arthritis and its comorbidities

Thirty-seven studies provided comorbidity and accompanying symptoms data for arthritic pain [166,176,177,179-181,185-187,190,194,200,202,206,207,210,212,213,217,219,220,222-224,227-232,234-240]. One study provided p value for the association with OR or percentage data [240]. This study was included but not described in the following comorbidity and accompanying symptom categories. Lee et al. reported separate comorbidity data for Beijing and Shanghai [166]. These two data were considered as two data, although they came from the same article. Arthritis was defined as having pain in the joints and included both OA and RA. The majority of the included studies reported findings for comorbid mental and behavioural disorders (21 studies), whereas one study reported findings for "blood and blood-forming organs and certain disorders involving the immune mechanism".

The main comorbidities/accompanying symptoms for arthritic pain included frequent or

severe headache, chronic back/neck problems, depression, panic attacks, PTSD, heart attack, heart disease, hypertension, asthma, any chronic pain, any physical diseases, and "any mental or physical disorders or pain".

The characteristics of the 37 included arthritic pain studies are presented in Table 3.26. Of the included studies, two recruited participants under 18 years [217,234], five did not describe the age of participants [177,187,231,232,234], and the remainder recruited adults. Eighteen studies recruited from the general public [166,176,177,185-187,190,202,206,217,222,224,229,231,232,234,238,240], 18 studies recruited arthritic patients [179-181,194,200,207,210,212,219,220,223,227,228,230,235-237,239]. Nineteen studies recruited participants from USA [176,177,181,185,186,200,202,210,212,217,219,223,224,227,228,232,234,237,239], four recruited from the Netherlands [187,220,230,240], two recruited from China [166,229], one study was a collaborative work of several countries [206], and the remaining studies recruited participants from other countries.

Table 3.26 Characteristics of included arthritic pain studies

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
Ayers et al. [237]	n=180, arthritis, from a university medical centre	Patients were scheduled for total knee replacement	USA	65.1 years
Ayoubi et al.[238]	n=177, G (33% arthritis and 67% controls who has never had musculoskeletal problems)	Patient's response to survey question of joints or musculoskeletal soft tissue problems	Lebanon	For the OA group: < 44 years: 15 (25.4%) 45-64 years: 34 (57.6%) ≥65 years: 10 (16.9%) For the control group: < 44 years: 30 (25.4%) 45-64 years: 68 (57.6%) ≥65 years: 20 (16.9%)
Baruth et al. [239]	n=152, arthritis, from a clinical trial	Patient's self report to survey questions which were comprehensive and may include lupus, infectious arthritis, and carpal tunnel syndrome	USA	57.0 ± 9.9 years
Bischoff-Ferrari et al. [181]	n=922, medicare beneficiaries	Patient's medicare claim of total hip replacement.	USA	73.1 ± 5.6 years
Black et al. [185]	n=3050, G (40.8% arthritis)	Patient's response to a checklist of chronic physical conditions	USA	Depressed group: 57.2±13.0 years.

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
		including arthritis		Not depressed group: 61.6±13.5 years.
Blackman et al. 2011 [217]	n=40465, G, children with chronic health conditions	Survey question asking presence of arthritis	USA	Age for the total population was not provided. The total population age provided was for a previous survey as an estimate of prevalence. For the Arthritis/other joint problems, the age category break down was as follows: 0-5 years old: 12.9±2.4 6-11 years old: 23.9±3.5 12-17 years old: 63.1±3.9
Blackman et al. 2013 [234]	n=91642, G with 1824 having arthritis.	Based on parental report of bone, joint, or muscle problems	USA	Did not describe
Braden et al. [186]	n=5689, G (27.9% arthritis, 33.5% chronic back/neck problems)	Patient's response to a checklist of arthritis/ rheumatism, chronic back or neck problems	USA	With lifetime self-reported pain: 18-44 years: 42.7% 45-64 years: 36.1% 65 years and older: 21.2% Without lifetime self-reported pain: 18-44 years: 63.3% 45-64 years: 25.0% 65 years and older: 11.4%
Buist-Bouwman et al. [187]	n=7076, G (9% chronic back trouble, 8.3% rheumatism)	Survey question asking presence of chronic back trouble or rheumatism	Netherland	Not described
Dominick et al. [231]	n=12488, G (24.2% neck/back disorder, 14.7% arthritis, 2.9% osteoporosis)	Patient's response to a checklist of CMP sites (via a list of pain regions)	New Zealand	Not described
Fernandez-de-Las-Penas et al. [190]	n=29478, G (7616 arthritis (25.8%), 6654 cervical pain (22.6%), 6793 LBP (23%), 1945 osteoporosis (6.6%))	Uncertain, authors only mention analysing presence of chronic diseases/symptoms	Spain	16-30 years: 4536 31-50 years: 11170 51-70 years: 8198 >70 years: 5574
Fitzgerald et	n=183, arthritis,	Based on 1986	USA	For the standard

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
al. [219]	from a university medical centre	American College of Rheumatology clinical criteria for knee OA and grade II Kellgren and Lawrence radiograph changes		exercise group (n=92): 64.6±8.4 years For agility and perturbation group (n=91): 63.3±8.9 years
Hoogeboom et al. [220]	n=401, arthritis, from a specialized hospital for orthopedics, rheumatology and rehabilitation	Inclusion criteria is not described, radiographs are taken for index joint of complaint and number of painful joint sites are recorded	Netherland	For OA without joint pain comorbidity (n=170): 57.7±13.7 years For OA with joint pain comorbidity (n=231): 58.4±12.2 years
Kauppila et al. [194]	n=88, arthritis, from surgical waiting list	Pre-defined criteria requiring the presence of OA	Finland.	70.7 (5.5) years
Klemenc-Ketiš et al. [222]	n=712, G who visits GP (15.7% osteoarthritis/ rheumatic diseases)	Questionnaire containing question asking presence of OA and rheumatic diseases	Slovenia	51.8 ±15.9 years
Lee et al. [166]	n=5201, G (8.6% arthritis from Beijing area, 15.3% arthritis from Shanghai area. Sample size not divided into Beijing/Shanghai areas)	Patient's response to a question on arthritis	China	Beijing: 18-29 years: 12.6% 30-44 years: 39.8% 45-59 years: 29.5% 60+ years: 18.1% Shanghai: 18-29 years: 19.3% 30-44 years: 33.9% 45-59 years: 32.4% 60+ years: 14.4%
Lee et al. 2012 [223]	n=176, arthritis, source of participants unclear	Inclusion criteria includes satisfying American College of Rheumatology criteria for RA	USA	21<45 years: 21.0% 45<65 years: 55.1% ≥65 years: 23.3% Mean age: 55 years
Ligthart et al. [240]	n=11948, twins and relatives of twins. Participants must have participated in the previous survey in order to be in the current survey (9.6% had chronic joints pain)	Survey question asking the location and frequency of pain.	Netherland	All participants: 44.5±15.7 years No pain: 43.4±16.3 years Occasional pain: 44.3±15.4 years Frequent pain: 45.7±16.2 years
Mangani et al. [200]	n=435, arthritis, within community dwelling persons	Knee pain and radiograph evidence of knee OA	USA	68.7±5.6 years

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
L. A. McWilliams & Higgins et al. [224]	n=5692, G (27.3% arthritis, 29.3% chronic SP)	Questionnaire containing question asking presence of arthritis, chronic neck/back problems	USA	52.1±11.2 years
Lachlan A. McWilliams & Bailey et al. [232]	n=5645, G (27.1% arthritis, 29.2% chronic back/neck problem)	Survey question asking presence of chronic back/neck problems or and arthritis	USA	Not described
McWilliams et al. 2003 [176]	n=5877, G (6.5% arthritis)	Survey question asking presence of "severe arthritis, rheumatism, or another bone or joint disease"	USA	Chronic pain group: mean 40.44±10.08 years General population group: mean 32.66±10.58 years
McWilliams et al. 2004 [177]	n=3032, G (19.4% arthritis, 20.3% back pain)	Survey question asking presence of chronic back pain and arthritis	USA	Not stated
Nilsdotter et al. [180]	n=281, arthritis (70%), and control group (30%) without hip complaints.	Patients had primary unilateral total hip replacement due to primary OA.	Sweden	OA group: 71 (50-92) years Reference group: 72 (50-90) years
Raab et al. [235]	n=344, arthritis, from an observational cohort study – adult juvenile idiopathic arthritis JuMBO	Patients were recruited if they fulfill International League of Associations for Rheumatology criteria for juvenile idiopathic arthritis	Germany	19.7±2.8 years
Rat et al. [236]	n=284, arthritis, from two multicentre cohorts of total hip/knee arthroplasty patients	OA according to American College of Rheumatology criteria and patients were scheduled for hip/knee arthroplasty.	France	For the 3 year follow up cohort (n=195): 72.4 ± 8.3 years For the 10 year follow up cohort (n=89): 73.3 ± 11.9 years
Sareen et al. [202]	n=5877, G (6.5% arthritis, rheumatism, or other bone/joint disease)	Patient's response to a checklist of question including arthritis	USA	Ranged from 15 - 54 years
Singh et al. (hip OA) [227]	n=13310, arthritis, from Mayo clinic, Rochester	Patients who have undergone total hip arthroplasty	USA	Mean age was 65 years. For the four groups, their mean age were as

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
				following: Primary total hip arthroplasty: Two year follow up: 65.0±13.3 years Five year follow up: 64.7±12.9 years Revision total hip arthroplasty: Two year follow up: 65.7±13.1 years Five year follow up: 64.6±13 years
Singh et al. (knee OA) [228]	n=13787, arthritis, from Mayo clinic total joint registry	Patients who had undergone total knee arthroplasty	USA	Mean age was 68 years. For the four groups, their mean age were as following: Primary total knee arthroplasty: Two year follow up: 68.0±10 years Five year follow up: 68.0±10 years Revision total knee arthroplasty: Two year follow up: 69.0±10 years Five year follow up: 69.0±10 years
Siu et al. [229]	n=1518, H	Uncertain, method of CMP identification not described in the publication	SAR, China	11-13 years: 34.7% 14-16 years: 49.1% 17-19 years: 16.2%
Stupar et al. [179]	n=1692, arthritis, from a population based cohort study in Southern Ontario, Canada	Pre-defined criteria requiring the patients to have significant pain and functional disabilities related to hip/knee joints.	Canada	71.7 years
Tamber et al. [213]	n=17,638, G born in 1970, 1960, 1955, 1940/41 and 1924/25 (3.9% have osteoporosis)	Survey question asking presence of osteoporosis	Norway	30 years: 34.5% 40 and 45 years:42.6% 59/60 years:50.9% 75/76 years:49.8%

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
Tsang et al. [206]	n=85,052, G (20% chronic SP, 16.5% arthritis)	Survey question asking presence of chronic back/neck problems, arthritis, and rheumatism	IntS	Mean age (overall): 42.9 years Mean age (developing countries): 38.2 years Mean age (developed countries): 45.5 years
Van Dijk et al. [207]	n=288, arthritis, from 3 rehabilitation centres and 2 hospitals	Diagnosis of hip or knee OA by MD based on radiograph findings or America College of Rheumatology clinical criteria	Did not specify. But authors were from Netherland.	66±8.7 years
Wesseling et al. [230]	n=979, arthritis, from a multicentre trial (Cohort Hip and Cohort Knee). Participants referred by GP and advertisement	Having pain or stiffness of the knee or hip	Netherland	56±5 years
Williams Russo et al. [212]	n=51, arthritis, undergoing total knee replacement from hospital	Participants have to be scheduled for knee replacement	USA	68±7.3 years (range: 48 - 84 years with 75% above 65 years)
Wolfe et al. [210]	n=22131, from national databank for rheumatic diseases, participants are recruited from rheumatologists, 7597 had RA.	Participants are diagnosed by US rheumatologists	USA	For RA, the participants' age are as following: Depressed: 57.2±13.0 years. Not depressed: 61.6±13.5 years.

IntS: International study including Colombia, Mexico, USA, Belgium, France, Germany, Italy, Netherlands, Spain, Ukraine, Israel, Lebanon, Nigeria, South Africa, Japan, PRC (Beijing and Shanghai),and New Zealand.
Six studies also provided data for chronic SP and had been included in the chronic SP section [186,187,190,206,229,231]

G: General population
GP: General practitioner
H: High school student
LBP: Low back pain
MD: Medical doctor
OA: Osteoarthritis
RA: Rheumatoid arthritis
SD: Standard deviation
USA: United state of America

3.3.4.1 Mental and behavioural disorders/symptoms as comorbidity/accompanying symptoms of arthritis

Twenty-one studies reported findings in this category [166,176,177,180,185-187,202,206,207,210,212,217,219,220,222,224,228,232,234,235] (Appendix 9). Of the 21 studies, two of them recruited children as participants [217,234] and one of them recruited teenager as participant [235]. The range of reported mental and behavioural disorder percentage was between 0% to 28.1% amongst adult participants (Table 3.28). One study reported the "incidence rate" and "cumulative risk" in nine years for depression to be 5.5 (95% CI 5.3-5.7) per 100 patient years, and 38.3% (95% CI 36.6-40.1%) respectively [210].

Amongst the children with arthritis, the percentage of comorbid mental and behavioural disorders/accompanying symptoms ranged from 10.8% to 38% (Table 3.27). Association wise, the overall results were conflicting among studies. For mental disorders, there were conflicting findings for dysthymia, major depressive disorder, GAD, any anxiety, panic disorder, simple phobia, social phobia, specific phobia, agoraphobia without panic, any mood disorders, and substance use (Table 3.28). The only certain findings were depression (OR ranged from 1.48-2.82), panic attacks (OR ranged from 2.00-2.09), and PTSD (OR ranged from 2.52-3.69) (Table 3.28). One study reported separate data for two surveyed sites and indicated no significant association between arthritis and alcohol dependence/abuse, and any substance use disorder [166] (Table 3.28). One study reported no association between arthritis and all mental disorders [166], drug abuse or dependence [166] (Table 3.28). Another study reported OR for depression-anxiety disorder was 1.6 [206], and a third study [186] reported the ORs for arthritis and suicidal ideation, plan, and attempt were between 1.4-2.0 (Table 3.28).

For children with arthritis, only one study reported the association with comorbid mental and behavioural disorders/accompanying symptoms [234]. Children with arthritis were at least three times more likely to have ADHD and at maximum of 5.1 times more likely to have depression.

Table 3.27 Summary of percentage data of comorbid mental and behavioural conditions or accompanying symptoms of children with arthritis

Mental and behavioural disorders/symptoms of children	Percentage among arthritis
Learning disability	38%
Difficulty with feeling anxious or depressed	33.4%
ADD/ADHD	22.1% and 29%
Behaviour problem at least 12 months	27.1%
Difficulty with behaviour problems, such as acting out, fighting, bullying or arguing	27.1%
Difficulties in learning, understanding or paying attention	26.0%
Long-term emotional, developmental or behavioural problem	25.9%
Depression	20.9%
Anxiety	20.3%
Difficulties in speaking, communicating or being understood	12.5%
Feels worthless or inferior:	10.8%
Unhappy, sad, or depressed	10.8%

Information extracted from [217,234]
ADD: Attention deficit disorder
ADHD: Attention deficit hyperactive disorder

Table 3.28 Summary of ORs range and percentage data of mental and behavioural disorders as comorbidities or accompanying symptoms of arthritis

Mental and behavioural disorders/symptoms of children	Study provided OR	ORs	Comparison group	Study provided percentage data	Percentage
Significant association					
PTSD	[176,202]	2.52 and 3.69	General public without arthritis	[166]	0% and 0.8%
Panic attacks	[177,202]	2.00 and 2.09	General public without arthritis	ND	
Depression	[176,177]	1.48 and 2.82	General public without arthritis	[210,219,220,222,228,235]	4.9-24%
Agoraphobia with or without panic	[176]	3.19	General public without arthritis	ND	
Anxiety based on Zung anxiety score ≥50	[222]	2.59	Compared to GP-visiting general public without osteoarthritis and rheumatic diseases		
Suicidal plan	[186]	2	General public without arthritis		
Depressive symptoms	[185]	1.87	General public without arthritis		
Substance use	[187]	1.8	Compared with general public without rheumatism		
Suicidal ideation	[186]	1.7	Compared with general public without arthritis		
Depression-anxiety disorder	[202]	1.6	General public without arthritis		
Suicide attempt	[186]	1.4	General public without arthritis		
No association					
Agoraphobia without panic		2.23 (0.97–5.11) (Sareen et al.) [202]	General public without arthritis	[166]	0%
Depression based on Zung depression score ⩾50		1.23 (0.62-2.41) (Klemenc-Ketiš et al.) [222]	Compared to GP-visiting general public without osteoarthritis and rheumatic diseases	ND	
Alcohol abuse or dependence		No association 1.9 (0.9-4.1) (Beijing) [166]	General public without arthritis	[166]	0.5% and 4.3%

Mental and behavioural disorders/symptoms of children	Study provided OR	ORs	Comparison group	Study provided percentage data	Percentage
		1.0 (0.2-5.6) (Shanghai) [166]			
Alcohol dependence		No association 2.4 (0.4-15.9) (Beijing) [166] 1.9 (0.3-13.2) (Shanghai) [166]	General public without arthritis	[166]	0.5% and 1.7%
Drug abuse or dependence		No association 2.6 (0.2-42.7) (Beijing) [166]	General public without arthritis	[166]	0% and 0.2%
Any substance use disorder		No association 1.9 (0.9-4.0) (Beijing) [166] 1.0 (0.2-5.4) (Shanghai) [166]	General public without arthritis	[166]	0.5% and 4.5%
Conflict results					
Any mood disorder		Conflicting result 1.7 (0.5-6.2) (Beijing) [166] 5.7 (1.3-26.1) (Shanghai) [166] 2.78 (2.06-3.75) [176] 1.5 (1.1-2.0) [187]	General public without arthritis/rheumatism	[166]	3.9% and 5.7%
All mental disorders		Conflicting result 1.6 (0.8-3.1) (Beijing) [166] 3.7 (1.2-11.4) (Shanghai) [166]	General public without arthritis	[166,187]	10% to 28.1%
Social phobia		Conflicting result 0.96 (0.66–1.39)	General public without arthritis	[166]	0%

Mental and behavioural disorders/symptoms of children	Study provided OR	ORs	Comparison group	Study provided percentage data	Percentage
		(Sareen et al.) [202] 1.92 (1.31-2.82) [176]			
Simple phobia		Conflicting result 1.22 (0.78–1.93) (Sareen et al.) [202] 2.20 (1.43-3.38) [176]	General public without arthritis	ND	
Specific phobia		Conflicting result 2.3 (0.5-10.5) (Beijing) [166] 6.9 (1.3-37.0) (Shanghai) [166]	General public without arthritis	[166]	3.5% and 7.5%
Major depression disorder alone or with hierarchy		Conflicting result 1.8 (0.5-6.6) (Beijng) [166] 8.0 (1.7-38.4) (Shanghai) [166]	General public without arthritis	[166]	3.9% and 5.7%
Dysthymia:		Conflicting result 4.0 (1.1-14.4) (Beijing) [166] 0.8 (0.1-8.0) (Shanghai) [166] 2.07 (1.26-3.42) [176]	General public without arthritis	[166]	0.3% and 1.1%
GAD:		Conflicting result 2.4 (1.3-4.5) (Beijing) [166] 15.4 (2.9-83.3) (Shanghai) [166] 1.13 (0.60–2.13) (Sareen et al.) [202] 2.17 (1.42-3.33) [177]	General public without arthritis	[166]	2.3% and 3.6%

Mental and behavioural disorders/symptoms of children	Study provided OR	ORs	Comparison group	Study provided percentage data	Percentage
		2.30 (1.45-3.67) [176]			
Any anxiety		Conflicting result 1.8 (0.7-4.5) (Beijing) [166] 5.9 (1.3-25.9) (Shanghai) [166] 2.86 (2.06-3.97) [176] 1.4 (1.1-1.8) [187] 2.28 (1.58-3.29) [202]	General public without arthritis/rheumatism	[166,222,228,235]	2% to 22.3%
Panic disorder with or without agoraphobia		Conflicting result 4.27 (2.39-7.61) [176] 1.0 (0.1-10.1) (Beijing) [166]	General public without arthritis	[166]	0% and 0.4%
Borderline personality disorder		ND	ND	[224]	27.3%
Psychiatric diseases/disorder				[180,207,212,235]	2.6% to 26.3%
Memory problems				[219]	8.2%

GAD: Generalized anxiety disorder
GP: General practitioner
ND: No data
PTSD: Post traumatic stress disorder

3.3.4.2 Diseases/symptoms of the circulatory system as comorbidities/accompanying symptoms of arthritis

Cardiovascular comorbidities

Sixteen studies reported findings for cardiovascular comorbidities/accompanying symptoms [166,176,180,194,200,207,212,219,220,227,228,230,235-237,239] (Table 3.29). The prevalence of cardiovascular diseases ranged from 0.3% to 79.5%. More specifically, the prevalence of cardiac insufficiency, hypertension, stroke, heart attack, and heart disease (not specified) ranged from 0.3% to 29.6%, 7.3% to 50.7%, 0.7% to 4.2%, 11.8% to 17.1%, and 4% to 54% respectively. One study reported the ORs for heart attack, heart disease, and high blood pressure ranged from 5.8-8.7, 3.1-4.0, and 2.0-2.7 respectively [166]. This study did not specify what heart disease referred to.

Table 3.29 Cardiovascular disorders comorbidity of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Kauppila et al. [194]	Cardiovascular disease: 70 (79.5%)	No data
Lee et al. [166]	Beijing participants: Stroke: 4.2% (SE: 2.1) Heart attack: 11.8% (SE: 2.4) Heart disease: 25.2% (SE: 6.0) High blood pressure: 25.5% (SE: 3.4) Shanghai participants: Stroke: 2.3% (SE: 1.9) Heart attack: 17.1% (SE: 5.1) Heart disease: 22.5% (SE: 4.8) High blood pressure: 24.6% (SE: 4.2)	Compared with general public without arthritis: Beijing: Stroke: 11.5 (2.9-45.5) Heart attack: 5.8 (3.5-9.7) Heart disease: 4.0 (2.1-7.6) High blood pressure: 2.7 (1.6-4.8) Shanghai: Heart attack: 8.7 (2.9-25.7) Heart disease: 3.1 (1.7-5.7) High blood pressure: 2.0 (1.3-3.0)
Van Dijk et al. [207]	Cardiac diseases: 54%	
Mangani et al. [200]	Hypertension: 44.1% Angina: 5.7% Myocardial infarction: 1.8% Other heart disease:13.8%	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
	Stroke: 0.7%	
McWilliam et al. 2003 [176]	High blood pressure: 24.6%	
Williams Russo et al. [212]	Hypertension: 43% Coronary artery disease (myocardial infarction or angina): 14% Cerebrovascular accident: 2%	
Fitzgerald et al. [219]	The percentage listed below are the combined results of both groups: High blood pressure: 86 (47.0%) Congestive heart failure: 1 (0.5%) Heart disease: 15 (8.2%) Stroke: 3 (1.6%)	
Hoogeboom et al. [220]	For hip and/or knee OA (n=401): 47 (12%) have cardiovascular disease	
Singh et al. (hip OA) [227]	Primary total hip arthroplasty: Two year follow up: Heart disease: 7% Five year follow up: Heart disease: 6% Revision total hip arthroplasty: Two year follow up: Heart disease: 6% Five year follow up: Heart disease: 4%	
Singh et al. (knee OA) [228]	Primary total knee arthroplasty: Two year follow up: Heart disease: 8% Five year follow up: Heart disease: 7% Revision total knee arthroplasty: Two year follow up: Heart disease: 7% Five year follow up: Heart disease: 5%	
Wesseling et al. [230]	For self-reported comorbidity of >1% prevalence: Hypertension: 198 (19.8%) Severe heart disease or myocardial infarction/stroke: 14 (1.4%)	
Raab et al. [235]	Cardiovascular diseases: 34 (9.9%) Hypertension: 25 (7.3%)	

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
	Cardiac insufficiency: 1 (0.3%)	
Rat et al. [236]	For the 3 year follow up cohort: Cardiac insufficiency: 29 (17.9%) For the 10 year follow up cohort: Cardiac insufficiency: 21 (29.6%)	
Ayers et al. [237]	Cardiac disease: 8.8%	
Baruth et al. [239]	hypertension: 50.7% stroke: 2.0%	
Nilsdotter et al. [180]	Heart: 9.2% Hypertension: 27.8%	

CI: Confidence interval
OA: Osteoarthritis
OR: Odds ratio
SE: Standard error

Vascular comorbidities

Five studies reported prevalence of vascular diseases [180,200,207,227,228]. The percentage of vascular comorbidities ranged from 2% to 25.6% (Table 3.30). The studies did not specify what kind of vascular diseases they were.

Table 3.30 Vascular disorder comorbidity of arthritis as comorbidity of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Van Dijk et al. [207]	Vascular diseases: 25.6%	
Mangani et al. [200]	Vascular disease: 12.6%	
Singh et al. (hip OA) [227]	Primary total hip arthroplasty: Two year follow up: Peripheral vascular disease: 4% Five year follow up: Peripheral vascular disease: 3% Revision total hip arthroplasty: Two year follow up: Peripheral vascular disease: 4% Five year follow up: Peripheral vascular disease: 3%	No data

Singh et al. (knee OA) [228]	Primary total knee arthroplasty: Two year follow up: Peripheral vascular disease: 5% Five year follow up: Peripheral vascular disease: 4% Revision total knee arthroplasty: Two year follow up: Peripheral vascular disease: 4% Five year follow up: Peripheral vascular disease: 2%	
Nilsdotter et al. [180]	Peripheral arteries: 12.7%	

CI: Confidence interval
OA: Osteoarthritis
OR: Odds ratio

3.3.4.3 Diseases/symptoms of the respiratory system as comorbiditie/accompanying symptoms of arthritis

There were 14 studies that reported data on respiratory disorders [166,176,180,194,200,207,212,219,220,227,228,230,235,237] (Table 3.31). The prevalence of respiratory disorders ranged from 0.5% to 28.8%. Asthma ranged from 7.6% to 12.6%, tuberculosis ranged from 0.5% to 3.2%, and chronic obstructive pulmonary disease ranged from 7% to 14%. The ORs for asthma ranged from 3.8 to 5.0 according to the report of Beijing and Shanghai from Lee et al. [166]. This report also showed conflict results for tuberculosis and "lung disease other than asthma and tuberculosis".

Table 3.31 Respiratory disorders comorbidity of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Kauppila et al. [194]	Pulmonary disease: 18 (20.5%)	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Lee et al. [166]	Beijing participants: Asthma: 8.2% (SE: 2.4) Tuberculosis: 3.2% (SE: 2.4) Seasonal allergies: 7.8% (SE: 2.2) Other lung disease: 2.2% (SE: 1.0) Shanghai participants: Asthma: 12.6% (SE: 5.2) Tuberculosis: 0.5% (SE: 0.4) Seasonal allergies: 12.4% (SE: 4.8) Other lung disease: 2.2% (SE: 1.6)	Compared with general public without arthritis: Beijing: Asthma: 5.0 (2.2-11.2) Tuberculosis: 8.9 (1.1-71.4) Other lung disease: 5.0 (1.0-24.8) Non-significant difference: *Seasonal allergies: 0.9 (0.5-1.8)* Shanghai: Asthma: 3.8 (1.0-13.7) Non-significant difference: *tuberculosis: 0.4 (0.0-3.1)* *Other lung disease: 5.7 (0.7-44.8)* *Seasonal allergies: 2.1 (0.8-5.1)*
Van Dijk et al. [207]	Respiratory diseases: 28.8%	
Mangani et al. [200]	Pulmonary disease: 8.3%	
McWilliam et al. 2003 [176]	Severe asthma, bronchitis, emphysema, tuberculosis, or other lung problems: 15.7%	
Williams Russo et al. [212]	Chronic obstructive pulmonary disease: 7 (14%)	
Fitzgerald et al. [219]	The percentage listed below are the combined results of both groups: Lung disease: 11 (6.0%)	
Hoogeboom et al. [220]	For hip and/or knee OA (n=401): 27 (7%) have respiratory disease	
Singh et al. (hip OA) [227]	Primary total hip arthroplasty: Two year follow up: Chronic obstructive pulmonary disease: 9% Five year follow up: Chronic obstructive pulmonary disease: 9% Revision total hip arthroplasty: Two year follow up: Chronic obstructive pulmonary disease: 7% Five year follow up: Chronic obstructive pulmonary disease: 7%	
Singh et al. (knee	Primary total knee arthroplasty:	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
OA) [228]	Two year follow up: Chronic obstructive pulmonary disease: 11% Five year follow up: Chronic obstructive pulmonary disease: 10% Revision total knee arthroplasty: Two year follow up: Chronic obstructive pulmonary disease: 9% Five year follow up: Chronic obstructive pulmonary disease: 9%	
Wesseling et al. [230]	For self-reported comorbidity of >1% prevalence: Asthma, chronic bronchitis, pulmonary emphysema or chronic non-specific lung disease: 90 (9.1%) Pharyngitis, sinusitis: 91 (9.0%)	
Raab et al. [235]	Pulmonary diseases: 28 (8.1%) Asthma: 26 (7.6%) Allergic diseases: 84 (24.4%) Allergic rhinitis: 50 (14.5%) House dust mite allergy: 16 (4.7%)	
Ayers et al. [237]	Pulmonary disease: 6.3%	
Nilsdotter et al. [180]	Lung: 0.5%	

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OA: Osteoarthritis
OR: Odds ratio
SE: Standard error

3.3.4.4 Endocrine, nutritional and metabolic diseases/symptoms as comorbidities/accompanying symptoms of arthritis

Fifteen studies reported data in this category [166,176,180,181,194,200,207,219,220,223,227,228,230,235,238] (Table 3.32). For prevalence, endocrinological diseases were reported to be between 0.4% to 69%, diabetes between 0.9% to 22.7%, thyroid diseases between 0.4% to 6.7% (hypothyroidism is reported as 2% [235]), obesity/overweight between 16.1% to 54.2%. The ORs,

according to Lee et al. [166], for diabetes and thyroid disease were conflicting. The Beijing data showed an association between arthritis and diabetes and thyroid disease whereas the Shanghai data showed no association.

Table 3.32 Endocrine disorders as comorbidities of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Kauppila et al. [194]	Diabetes: 20 (22.7%) Endocrine disease: 20 (22.7%)	No data
Lee et al. [166]	Beijing participants: Diabetes or high blood sugar: 16.5% (SE: 5.9) Thyroid disease: 4.0% (SE: 1.6) Shanghai participants: Diabetes or high blood sugar: 7.4% (SE: 4.1) Thyroid disease: 0.4% (SE: 0.4)	Compared with general public without arthritis: Beijing: Diabetes or high blood sugar: 5.3 (1.9-14.8) Thyroid disease: 5.1 (1.6-15.1) Shanghai: *Diabetes or high blood sugar: 2.2 (0.6-7.7)* *Thyroid disease:0.4 (0.0-6.0)*
Van Dijk et al. [207]	Endocrine and metabolic disease: 46% Overweight (body mass index 25-30): 51.7% Obesity: 23.6%.	
Mangani et al. [200]	Obesity: 52.9% Diabetes: 9.2%	
McWilliam et al. 2003 [176]	Diabetes: 5.5%	
Fitzgerald et al. [219]	The percentage listed below are the combined results of both groups: Diabetes: 11 (6.0%)	
Hoogeboom et al. [220]	For hip and/or knee OA (n=401): 28 (7%) have diabetes	
Lee et al. [223]	31% of participants were obese	
Singh et al. (hip OA) [227]	Primary total hip arthroplasty: Two year follow up: Diabetes (with or without organ damage): 6% Five year follow up: Diabetes (with or without organ damage): 5% Revision total hip arthroplasty: Two year follow up: Diabetes (with or without organ damage):	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
	7% Five year follow up: Diabetes (with or without organ damage): 7%	
Singh et al. (knee OA) [228]	Primary total knee arthroplasty: Two year follow up: Diabetes (with or without organ damage): 9% Five year follow up: Diabetes (with or without organ damage): 8% Revision total knee arthroplasty: Two year follow up: Diabetes (with or without organ damage): 10% Five year follow up: Diabetes (with or without organ damage): 7%	
Wesseling et al. [230]	For self-reported comorbidity of >1%: Obesity:161 (16.1%) Diabetes mellitus: 35 (3.5%) Thyroid disease: 53 (5.3%)	
Raab et al. [235]	Thyroid/endocrine diseases: 23 (6.7%) Hypothyroidism: 7 (2%) Hashimoto thyroiditis: 4 (1.2%) Diabetes mellitus: 3 (0.9%) Amyloidosis: 3 (0.9%)	
Ayoubi et al.[238]	Obesity (body mass index ≥30): 32 (54.2%) in OA 19 (16.1%) in controls (p=0.008)	
Nilsdotter et al. [180]	Diabetes: 7.1%	
Bischoff-Ferrari et al. [181]	Body mass index > 30: 25%	
Baruth et al. [239]	High cholesterol: 42.4%	

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OA: Osteoarthritis
OR: Odds ratio
SE: Standard error

3.3.4.5 Diseases/symptoms of the musculoskeletal system and connective tissue as comorbidities/accompanying symptoms of arthritis

Sixteen studies reported data on musculoskeletal pain comorbidities (Table 3.33) [166,179-181,190,194,207,219,220,227,228,230,235-237,239]. Only one study reported OR for chronic back/neck problems [166], the other studies all reported percentage data. Percentage of back/neck pain ranged from 6% to 69%, osteoporosis ranged from 3.2% to 13.9%, whereas other musculoskeletal comorbidities/accompanying symptoms ranged from 6.6% to 100%. Arthritic patients were 6.5 to 7.9 times more likely to have chronic back/neck problems [166]. Lee et al. did not make a clear differentiation between arthritis and chronic SP [166]. The comorbid chronic SP may well overlap with spinal joints regions. Other studies recruited OA of knee and/or hip [179-181,194,207,219,220,227,228,230,237] and some did not specify the location or included all the possible arthritic joints [166,190,235,236,239].

Table 3.33 Musculoskeletal pain as comorbidities/accompanying symptoms of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Kauppila et al. [194]	Osteoarthritis of other joints: 80 (90.9%) Osteoporosis: 9 (10.2%)	No data
Lee et al. [166]	Beijing participants: Chronic back/neck pain: 69.1% (SE: 5.4) Shanghai participants: Chronic back/neck pain: 61.0% (SE: 5.0)	Compared with general public without arthritis: Beijing: Chronic back/neck problems: 6.5 (3.4-12.4) Shanghai: Chronic back/neck problems: 7.9 (4.5-13.9)
Van Dijk et al. [207]	Diseases of bones, joints, muscle and skin: 100%	
Stupar et al. [179]	Prevalence of back pain amongst different OA: Hip only: 121 (62%) Knee only: 295 (45%) Both hip and knee: 514 (71%)	
Fernandez-de-Las-Penas et al. [190]	Prevalence of neck pain within arthrosis: 47.5% (46.0-49.1) Prevalence of LBP within arthrosis: 46.3% (44.8-47.8)	
Fitzgerald et al. [219]	The prevalence listed below are the combined results of both groups: Back pain: 88 (48.1%)	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
	Previous hip fracture: 2 (1.1%)	
Hoogeboom et al. [220]	For knee OA group (n=284): Spine pain: Lumbar: 66 (23%) Thoracic: 18 (6%) Neck: 49 (17%) Extremity pain (single and both sides are reported together): Shoulder: 47 (17%) Elbow: 20 (7%) Wrist: 26 (9%) Hand: 39 (14%) Hip: 41 (14%) Knee: 241 (85%) Ankle: 31 (11%) Foot: 39 (14%) For hip OA group (n=117): Spine pain: Lumbar: 43 (37%) Thoracic: 12 (10%) Neck: 18 (15%) Extremity pain (single and both sides are reported together): Shoulder: 17 (16%) Elbow: 5 (5%) Wrist: 9 (9%) Hand: 10 (10%) Hip: 95 (81%) Knee: 36 (33%) Ankle: 12 (12%) Foot: 13 (13%)	
Singh et al. (hip OA) [227]	Primary total hip arthroplasty : Two year follow up: Connective tissue disease: 6% Five year follow up: Connective tissue disease: 6% Revision total hip arthroplasty: Two year follow up: Connective tissue disease: 8% Five year follow up: Connective tissue disease: 8%	
Singh et al. (knee OA) [228]	Primary total knee arthroplasty: Two year follow up: Connective tissue disease: 7%	

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
	Five year follow up: Connective tissue disease: 8% Revision total knee arthroplasty: Two year follow up: Connective tissue disease: 8% Five year follow up: Connective tissue disease: 8%	
Wesseling et al. [230]	For self-reported comorbidity of >1% prevalence: Disorders of neck, shoulder, elbow, wrist or hand: 222 (22.2%) Back disorders (including slipped disc): 172 (17.2%) Chronic inflammation of joints (such as RA): 37 (3.7%) Other chronic rheumatic diseases, longer than 3 months: 29 (2.9%)	
Raab et al. [235]	Osteoporosis: 11 (3.2%)	
Rat et al. [236]	For the 3 year follow up cohort: Back pain: 91 (54.2%) For the 10 year follow up cohort: Back pain: 46 (59.0%)	
Ayers et al. [237]	Moderate to severe pain in the following areas: Non-operatively treated knee : 41 (23%) Ipsilateral hip: 36 (20%) Contralateral hip: 16 (9%) Low back: 46 (26%)	
Baruth et al. [239]	Osteoporosis: 13.9%	
Nilsdotter et al. [180]	Low back pain: 21.5% Unilateral hip pain: 20.2% Regional pain: 59.1% Widespread pain: 6.6%	
Bischoff-Ferrari et al. [181]	Other joint replacement or other revision: 39% (out of 828) Pain in back of lower extremity: 60% (out of 795)	

CI: Confidence interval
LBP: low back pain
OA: Osteoarthritis
OR: Odds ratio
RA: Rheumatoid arthritis
SE: Standard error

3.3.4.6 Diseases/symptoms of the nervous system as comorbidities/accompanying symptoms of arthritis

Eight studies reported findings for neurological comorbidities [166,180,194,207,220,229,230,235] (Table 3.34). The percentage of neurological conditions ranged from 0% to 76.2%. Specifically, epilepsy or seizures ranged from 0% to 1.5%. Siu et al. reported percentages of sleep disturbances amongst teenagers suffering from arthritis [229]. The percentage of sleep disturbances ranged from 64.2% for arthritis in arm to 76.2% for arthritis in shoulder. There was one study provided data for fatigue [220]. Of the participants, 44% of them scored more than 35 on the Checklist Individual Strength [969] which indicated severe fatigue.

There were conflicting results from Lee et al. [166] for neurological conditions. The Beijing data showed an association whereas the data from Shanghai showed no association between arthritis and neurological conditions. Epilepsy or seizures was shown to have no association with arthritis and was reported by the Beijing site but no data was available from Shanghai site [166].

Table 3.34 Neurological disorders as comorbidity/accompanying symptom of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Kauppila et al. [194]	Neurologic disease: 15 (17%)	No data
Lee et al. [166]	Beijing participants: Neurological problems: 1.7% (SE:1.6) Epilepsy or seizures: 1.3% (SE:1.2) Shanghai participants: Neurological problems: 0.3% (SE:0.3) Epilepsy or seizures: 0%	Compared with general public without arthritis: Beijing: Neurological problems: 19.2 (1.8-208.2) Shanghai: *Neurological problems: 0.6 (0.0-6.4)* Beijing participants reported non-significant difference between arthritic and non-arthritic participants for the following physical disorders: *epilepsy or seizures: 4.8 (0.3-79.8).*
Van Dijk et al. [207]	Neurological disease: 31.9%	No data

Siu et al. [229]	Percentage of sleep disturbance amongst teenagers with a particular type of chronic pain are listed below: Shoulder (n=115): 76.2% Arm (n=70): 64.2% Muscle (n=118): 70.0% Foot (n=87): 65.3% Limb (n=5): 74.6%	
Wesseling et al. [230]	For self-reported comorbidity of >1% prevalence: Dizziness with falls: 17 (1.7%)	
Raab et al. [235]	Neurologic diseases: 41 (11.9%) Epilepsy: 5 (1.5%)	
Hoogeboom et al. [220]	44% of them scored more than 35 on the Checklist Individual Strength which indicated severely fatigue	
Nilsdotter et al. [180]	Neurological disease: 2.0%	

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.4.7 Diseases/symptoms of the digestive system as comorbidities/accompanying symptoms of arthritis

Gastrointestinal comorbidity

Eight studies reported findings on the digestive system [166,176,180,207,219,220,230,235] (Table 3.35). The prevalence of digestive issues ranged from 0.3% to 34.7%. More specifically, ulcers in the digestive system, including “peptic ulcer” “duodenal ulcer” and/or “ulcerative colitis”, ranged from 0.3% to 11%. There was no association between arthritis and ulcer in stomach or intestine.

Liver and gallbladder comorbidity

Five studies provided data for comorbid liver and gallbladder diseases [176,207,219,230,235]. The percentage of liver diseases was 0.9% to 7.4% (the exact liver diseases were not specified) whereas the percentage of stomach or gall bladder disorders was between 0.9% to 9.7% (the exact gall bladder or stomach disorders were not specified). The percentage of cholelithiasis

was 1.8% [230]. Hoogeboom et al. (n=401) also described the prevalence of kidney/liver diseases was 1% [220].

Table 3.35 Diseases/symptoms of the digestive system as comorbidities/accompanying symptoms of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Lee et al. [166]	Beijing participants: Ulcer in stomach or intestine: 5.4% (SE: 3.5) Shanghai participants: Ulcer in stomach or intestine: 11.0% (SE: 2.7)	Compared with general public without arthritis: Beijing: *Ulcer in stomach or intestine:1.6 (0.5-5.9)* Shanghai: *Ulcer in stomach or intestine: 1.3 (0.7-2.4)*
Van Dijk et al. [207]	Upper gastrointestinal disease: 34.7% Lower gastrointestinal disease: 30.5% Liver diseases: 7.4%	
McWilliams et al. 2003 [176]	Chronic stomach or gall bladder trouble: 9.7%	
Fitzgerald et al. [219]	The prevalence listed below are the combined results of both groups: Stomach ulcer: 14 (7.7%) Liver disease: 2 (1.1%)	
Hoogeboom et al. [220]	Gastrointestinal complaints: 32 (8%)	
Wesseling et al. [230]	Cholelithiasis: 18 (1.8%) Peptic ulcer or duodenal ulcer: 14 (1.4%)	
Raab et al. [235]	Gastrointestinal diseases: 14 (4.1%) Crohn's disease: 4 (1.2%) Ulcerative colitis: 3 (0.9%) Gastrointestinal ulcer: 1 (0.3%) Liver and gallbladder disease: 3 (0.9%)	
Nilsdotter et al. [180]	Peptic ulcer: 1.5%	No data

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OA: Osteoarthritis
OR: Odds ratio
SE: Standard error

3.3.4.8 Diseases/symptoms of the eye and adnexa as comorbidities/accompanying symptoms of arthritis

Six studies reported findings on eye and adnexa disorders [166,176,180,207,235,236] (Table 3.36). The prevalence of eye and adnexa diseases/symptoms ranged from 0.9% to 96.1%. Apart from seasonal allergies where the percentage ranged from 7.8% to 12.4%, there was no specific eye and adnexa disease reported by more than one study. One study reported no association between seasonal allergies and arthritis [166].

Table 3.36 Diseases/symptoms of the eye and adnexa as comorbidities of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Lee et al. [166]	Beijing participants: Seasonal allergies: 7.8% (SE: 2.2) Shanghai participants: Seasonal allergies: 12.4% (SE: 4.8)	Compared with general public without arthritis: Beijing: *Seasonal allergies: 0.9 (0.5-1.8)* Shanghai: *Seasonal allergies: 2.1 (0.8-5.1)*
Van Dijk et al. [207]	Eye, ear, nose, throat and larynx disease: 96.1%	
McWilliam et al. 2003 [176]	Blindness, deafness, or severe visual or hearing impairment: 9.9%	
Raab et al. [235]	Eye diseases: 80 (23.3%) Uveitis: 59 (17.7%) Cataract: 3 (0.9%) Glaucoma: 9 (2.6%) Other eye diseases: 8 (1.6%)	
Rat et al. [236]	For the 3 year follow up cohort: Visual impairment: 51 (31.1%) For the 10 year follow up cohort: Visual impairment: 23 (31.9%)	
Nilsdotter et al. [180]	Vision problems: 1.5%	No data

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.4.9 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified and migraine as accompanying symptom of arthritis

Four studies reported data on headache/migraine [166,190,230,235] and one study reported data on dizziness/faintness [213] as an accompanying symptom of arthritis. Those who had arthritis were two to five times more likely to also have headache, 2.35 times to have migraine, and 2.38 times to have dizziness/faintness during the last week (Table 3.37). The chance of accompanying headache or migraine ranged from 8.7% to approximately 20%, and the chance of having dizziness/faintness during the last week was 47.2%.

Table 3.37 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified and migraine as comorbidity/accompanying symptoms of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Lee et al. [166]	Beijing participants: Frequent or severe headaches: 14.0% (SE: 2.7) Shanghai participants: Frequent or severe headaches: 19.8% (SE: 5.8)	Compared with general public without arthritis: Beijing: Frequent or severe headache: 2.1 (1.2-3.7) Shanghai: Frequent or severe headache : 4.8 (2.2-10.7)
Fernandez-de-Las-Penas et al. [190]	Migraine: 18.89%	Compared with general public without arthritis: Migraine: 2.35 (2.13 - 2.60)
Wesseling et al. [230]	Migraine or chronic headache: 124 (12.4%)	
Raab et al. [235]	Migraine: 30 (8.7%)	No data
Tamber et al. [213]	Dizziness/faintness during the last week: 47.2%	Compared with general public without arthritis: Dizziness/faintness during the last week: 2.38 (2.03-2.78)

CI: Confidence interval
OR: Odds ratio
SE: Standard error

3.3.4.10 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism as comorbidities of arthritis

One study reported data for blood diseases [235]. Raab et al. included 344 adults who had previously been diagnosed with juvenile idiopathic arthritis recruited from a biological register "JuMBO". Of them, 6.7% had haematological diseases, the study did not specify the kind of haematological diseases, 3.2% had anaemia, and 1.7% had iron deficiency.

3.3.4.11 Other findings

Eleven studies reported findings for the other category [166,176,179,180,186,194,200,219,231,234,239] (Table 3.38). The percentage for any physical or mental diseases ranged from 0% to 85.2%. The percentage of one other chronic pain ranged from 45.2% to 73.4%. The percentage of cancer ranged from 0% to 14.8%. Lee et al. [166] reported findings from both Beijing and Shanghai and found the percentage for "malaria or other parasitic diseases", or HIV ranged from 0.4% to 1.3%, and 0% to 0% respectively. The percentage of comorbidity/accompanying symptom reported by single studies included other chronic diseases (44.3%) [194], more than one lifetime pain conditions (39.1%) [186], and "ulcer, lupus, thyroid disease, or other autoimmune disorders" (5.5%) [176]. Blackman et al. reported data on functioning of behaviour, social, school, and home, of children [234]. For behavioural, social, and school functioning of arthritic children, at least 40% of the children showed positive functioning and less than 37% of them showed negative functioning. For home functioning, only 27.2% of children exercised everyday, at least 40% of children have enough sleep, and read for pleasure less than 30 mins/day.

The OR reported by Lee et al. [166] for any physical disease, and "any mental or physical disorders, pain", ranged between 2.3-3.1, and 4.0-6.2 respectively. The OR for chronic pain in arthritic pain was between 2.1 and 6.3. And there was no association between arthritis and "malaria or other parasitic diseases", or cancer.

Table 3.38 Other findings of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
Kauppila et al. [194]	Other chronic disease: 39 (44.3%)	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
Lee et al. [166]	Beijing participants: Any chronic pain: 73.4% (SE: 5.3) Any physical diseases: 54.7% (SE: 7.4) Any mental or physical disorders, pain: 85.2% (SE: 5.7) Malaria or other parasitic diseases: 0.4% (SE: 0.4) Cancer: 0% HIV: 0% Shanghai participants: Any chronic pain: 64.8% (SE: 5.1) Any physical diseases: 57.2% (SE: 7.4) Any mental or physical disorders, pain: 79.9% (SE: 4.2) Malaria or other parasitic diseases: 1.3% (SE: 0.2) Cancer: 0.6% SE: (0.6) HIV: 0%	Compared with general public without arthritis: Beijing: Any chronic pain (chronic pain anywhere): 6.1 (3.0-12.5) Any physical diseases: 3.1 (1.6-6.0) Any mental or physical disorders, pain: 6.2 (2.2-17.7) *Malaria or other parasitic diseases: 0.5 (0.0-5.7)* Shanghai: Any chronic pain (chronic pain anywhere): 6.3 (3.4-11.6) Any physical diseases: 2.3 (1.2-4.3) Any mental or physical disorders, pain: 4.0 (2.3-7.0) *Malaria or other parasitic diseases: 3.3 (0.2-57.5)* *Cancer: 3.1 (0.3-35.4)*
Braden et al. [186]	More than one lifetime pain condition: 39.1%	
Mangani et al. [200]	Cancer: 4.6%	No data
Stupar et al. [179]	No data	Compared to arthritic patients without LBP: Low back pain group included more females, had more comorbidities, had a greater number of troublesome joints, and reported more pain and disability. Low back pain was associated with worse pain and function at follow-up (3-5 years) (β=6.59; 95% CI, 4.36-8.81; P<0.001)
McWilliam et al. 2003 [176]	Ulcer, lupus, thyroid disease, or other autoimmune disorders: 5.5%	
Fitzgerald et al. [219]	The prevalence listed below are the combined results of both the standard exercise group and "agility and perturbation" group: Cancer: 27 (14.8%)	No data
Dominick et al. [231]	Percentage of chronic pain within CMP:	Compared with general public without arthritis:

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
	Arthritis: 45.2% Osteoporosis: 49.2%	The OR for chronic pain after adjusted for sociodemographic variables and the physical and mental conditions: Arthritis: 3.9 (3.3-4.6) Osteoporosis: 2.1 (1.5-2.8) Chronic pain is defined as pain lasted more than six months and may be in any parts of the body ranging from head to toes and including chest, stomach, and pelvic pain.
Blackman et al. 2013 [234]	Of the chronic bone, joint, muscle problem children, their percentage for the following emotional and behavioural problems are listed below: Behavioural functioning: Positive: Shows respect for teachers and neighbors: 86.9% (SE: 2.6) Gets along well with other children: 80.1% (SE: 3.1) Negative: Argues too much: 33.5% (SE: 3.4) Is disobedient: 9.6% (SE: 2.1) Is stubborn, sullen, or irritable: 21.8% (SE: 3.1) Social functioning: Positive: Tries to understand other people's feelings: 68.5% (SE: 3.3) Tries to resolve conflicts with classmates, family, or friends: 60.8% (SE: 3.3) Play sports: 44.3% (SE: 3.2) Participate in clubs: 56.6% (SE: 3.1) Negative: Bullies or is cruel or mean to others: 6.8% (SE: 2.0) Is withdrawn, and does not get involved with others: 3.2% (SE: 0.5)	
	School functioning:	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
	Positive: Cares about doing well in school: 87.5% (SE: 0.3) Does all required homework: 79.1% (SE: 2.6) Negative: Missed ≥ 10 days of school: 31% (SE: 3.2) School contacted >1 time: 36.7% (SE: 3.4) Repeat grade: 23.9% (SE: 3.3) Home functioning: Get enough sleep 7 days per week: 53% (SE: 3.2) Exercise every day: 27.2% (SE: 3) Read for pleasure ≤ 30 minutes per day: 43.7% (SE: 3.1)	
Baruth et al. [239]	Cancer: 12.7%	
Nilsdotter et al. [180]	Cancer: 5.6%	

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
CMP: Chronic musculoskeletal pain
LBP: Low back pain
OR: Odds ratio
SE: Standard error

3.3.4.12 Diseases/symptoms of the genitourinary system or ear and mastoid process as comorbidities or accompanying symptoms of arthritis

Ten studies reported percentage data for renal disorders [180,200,207,219,220,227,228,230,235,237] (Appendix 12). The prevalence of renal disease ranged from 0% to 11.2% and the percentage for urogenital disease was 44.4%. For gynaecological diseases, the percentage ranged between 4.2% to 5%. There was no specific genitourinary disease reported by more than one study.

Two studies reported the percentage of ear, nose, throat, and eye disorders ranged from 7.8% to 96.1% without reporting OR data [176,207] (Appendix 13).

3.3.5 Widespread pain and its comorbidities

Fourteen studies provided data for fibromyalgia/widespread pain [182,184,189,196,201,203,204,210,214,216,218,225,226,241]. The main comorbidities/accompanying symptoms for widespread pain included depression, anxiety, fatigue, irritable bowel syndrome, and irritable bladder.

The characteristics of the 14 included widespread pain studies are presented in Table 3.39. Except for one study that recruited participants from a national databank for rheumatic diseases [210], and three other studies that recruited adult women, twins, or from the general population [201,203,204], the remaining studies recruited fibromyalgia patients and these studies identified fibromyalgia either by meeting American College of Rheumatology criteria 1990 for fibromyalgia diagnosis or diagnosed by doctors. Most of the included studies recruited participants from USA and/or Canada [184,201,203,210,216,226], three recruited participants from Italy [189,214,241], and the remaining studies recruited from other countries or did not describe the country. All of the studies recruited adult participants with one study recruited twins [203], three recruited adult women [182,201,241], and one study recruited participants aged 31 years old and born on 1966 [204].

Table 3.39 Characteristics of included widespread pain/fibromyalgia studies

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
Aguglia et al. [214]	n=30, fibromyalgia, from rheumatology unit in hospital	Meeting American College of Rheumatology criteria 1990 for fibromyalgia diagnosis	Italy	58.33±13.43 years
Arnold et al. [216]	n=1025, fibromyalgia, source of participants not described	Meeting American College of Rheumatology criteria 1990 for fibromyalgia diagnosis	USA and Canada	Placebo group: 48.7±10.6 years Milnacipran group: 49.1±10.8
Bernatsky et al. [184]	n=99, fibromyalgia, from rheumatology clinics and from the community	Primary fibromyalgia fulfilling American College of Rheumatology criteria 1990	Canada	50.8±10.2 years
Carbonell-Baeza	n=118,	Meeting American	Spain	51.9±7.3 years

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
et al. [218]	fibromyalgia, from local association of fibromyalgia	College of Rheumatology criteria 1990 for fibromyalgia diagnosis		
Ciapparelli et al. [189]	n=117, fibromyalgia, from rheumatology clinic	Meeting American College of Rheumatology criteria 1990 for fibromyalgia diagnosis	Italy	52.0± 12.5 years
Kurtze et al. [196]	n=1816, fibromyalgia	Self-reported fibromyalgia that is informed by a doctor	Norway	The mean age of fibromyalgia patients without comorbidity was 48.63±11.02 years whereas the fibromyalgia patients with comorbidity were 56.36±12.40 years. The mean age of the other general population not having fibromyalgia was not listed.
Raphael et al. [201]	n=1312, AW	Questions on 1) pain lasting at least 1 week 2) axial skeletal pain 3) limb pain on the right and left side. Participants fulfilling the above 3 criteria are considered to have fibromyalgia-like symptoms	USA	Not mentioned.
Rehm et al. [225]	n=3035, fibromyalgia, from GP, orthopaedist, rheumatologist, and pain specialists clinics	American College of Rheumatology criteria	Germany	52.1±11.2 years
Schur et al. [203]	n=3982, T (2% fibromyalgia)	Self-reported fibromyalgia that is informed by a doctor	USA	32.4 ±14.7 years
Shillam et al. [226]	n=171, fibromyalgia,	Patients diagnosed with fibromyalgia	USA and Canada	60.7 ± 6.2 (range: 50-76) years

Study	Sample size/types of participant	Method of CMP identification	Country of study	Age of participants
	from fibromyalgia database of community living fibromyalgia patients	who was diagnosed clinically or participated in previous fibromyalgia clinical trials	(Pacific Northwest region)	
Sipila et al. [204]	n=5969, G (32.6% widespread pain)	Widespread pain defined as pain involving at least 1 upper extremity, 1 lower extremity, and either neck, back , or chest	Finland	Not mentioned. But sounds like 31 years old as authors, in 1997, contacted cohort who were born in 1966.
Wolfe et al. [210]	n=22131, from national databank for rheumatic diseases, participants are recruited from rheumatologists. 2674 had fibromyalgia	Participants are diagnosed by USA rheumatologists	USA	For RA, the participants' age are as following: Depressed: 57.2±13.0 years. Not depressed: 61.6±13.5 years. Age of fibromyalgia participants was not provided.
Bazzichi et al.[241]	n=140, fibromyalgia, from rheumatology division of Pisa university	Clinically classified by a rheumatologist based on 1990 American College of Rheumatology criteria	Italy	47.8 ± 8.8 years
Tikiz et al. [182]	n=100, fibromyalgia, source of participants not described	Based on criteria of American College of Rheumatology	Not described, but participants completed questionnaire in Turkey	Healthy control: 37.2 ± 10.3 years Only fibromyalgia: 42.9 ± 9.1 years Fibromyalgia plus major depression: 39.6 ± 10.1 years

AW: Adult women in the general population
G: General population
GP: General practitioner
RA: Rheumatoid arthritis
T: Twins
USA: United states of America
Two studies also provided data for chronic SP and had been included in the chronic SP section [188,197]

3.3.5.1 Mental and behavioural disorders/symptoms as comorbidities/accompanying symptoms of widespread pain

Twelve studies reported finding in this category [182,184,189,196,201,203,204,210,214,216,225,226,241] (Table 3.40).

They reported the percentage range of depression/depressiveness was between 5% to 90.9%, anxiety between 1% to 77.7%. Based on BDI, Patient Health Questionnaire, and Hamilton rating scale for depression, at the very least more than 11% of fibromyalgia patients had moderate depression. The percentages of other reported conditions/accompanying mental symptoms ranged from 2.6% to 67%. The ORs for PTSD, PTSD associated symptom clusters, panic attacks, or major depression ranged from 2.22 to 9.0.

Table 3.40 Mental disorders as comorbidities of fibromyalgia

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
Raphael et al. [201]	Approximately 6 months after the WTC terrorist attacks, 4.8% (N = 64) of the sample reported current symptoms consistent with a diagnosis of PTSD.	Female general public residing in New York/New Jersey metropolitan area, USA with fibromyalgia-like symptoms were compared to female general public without fibromyalgia-like symptom: Probable PTSD symptoms at follow-up: 3.39 (1.82-5.99). Among those with fibromyalgia-like symptoms at follow-up, PTSD was more likely among those reporting higher levels of pain interference (OR = 1.25 for a 10-point increase, 95% CI = 1.02–1.52, p < 0.05). *Higher levels of pain severity: 1.26 (for a 10-point increase) (0.99–1.62, p < 0.10)* For PTSD symptom clusters: avoidance/numbing: 2.22 (1.45-3.40) Increased arousal (OR 2.85 95% CI 1.98-4.09). But not "at a greater risk for event re-experiencing"
Sipila et al. [204]	Of the widespread pain patients, 30.4% (n=1477) of them have depression.	Compared with general public:

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
	Of the patients with both facial and widespread pain (n=469), the depression prevalence becomes 27.3% (n=128).	Depressiveness was associated with widespread pain (PPR 2.37, 95% CI 2.09-2.69).
Schur et al. [203]	No data	Compared to twins within the Twin Registry without fibromyalgia: Major depression: 6.1 (6.3-6.9) Panic attacks: 4.2 (3.5-5.0) PTSD: 9.0 (7.6-10.8)
Kurtze et al. [196]	Anxiety: 1411 (77.7%) Depression: 1650 (90.9%)	No data
Bernatsky et al. [184]	Depression: 9 (5%) Anxiety: 1 (1%)	
Ciapparelli et al. [189]	Of the 117 participants, they have life time prevalence of the following diseases: Psychiatric comorbidity: 86 (73.5%) Major depression: 59 (50.4%) Anxiety disorders: 26 (22.2%) -Panic disorder: 16 (13.7%) -GAD: 10 (8.5%) Eating disorder: 5 (4.3%) And the current prevalence of the following diseases: Psychiatric comorbidity: 50 (42.7%) Major depression: 39 (33.3%) Anxiety disorders: 14 (12%) -Panic disorder: 9 (7.7%) -GAD: 5 (4.3%) Eating disorder: 3 (2.6%)	
Aguglia et al. [214]	83.3% of patients had clinically significant depressive symptoms, corresponding to a Hamilton rating scale for depression total score>7.	
Arnold et al. [216]	Based on BDI score where below 10 is no/minimal depression, 10 to 18 is mild depression, and 19 to 25 is moderate depression. There were 599 (58%) with no/minimal depression, 317 (31%) with mild depression, 109 (11%) with moderate depression.	
Rehm et al. [225]	Based on the PHQ-9 score, 208 (6.8%) of the were not diagnosed with depression (PHQ-9 score: 0-4), 828 (27.3%) of them	

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
	were diagnosed with mild depression (PHQ-9 score: 5-9), 1556 (51.3%) of them were diagnosed with moderate depression (PHQ-9 score: 10-19), and 443 (14.6%) of them were diagnosed with moderately severe depression (PHQ-9 score: 20-27). Based on PHQ-9 score, 545 (18%) of participants have panic/anxiety disorder.	
Shillam et al. [226]	Anxious: 123 (72%) Sad: 114 (67%) Easily angered: 94 (55%) Fear of symptoms worsening: 93 (54%) Feel like a burden to others: 66 (39%)	
Wolfe et al. [210]	There were 2674 fibromyalgia participants, 37.9% (95% CI 36.1-39.8%) have self-reported depression.	
Bazzichi et al.[241]	There were 100 fibromyalgia patients Lifetime psychiatric comorbidity: Major depression: 20% Bipolar disorder: 2% Panic disorder: 12% Current psychiatric comorbidity: Major depression: 8% Bipolar disorder: 9% Panic disorder: 7%	
Tikiz et al. [182]	Of the fibromyalgia patients (n=67), 27 (40.2%) had major depression.	

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
GAD: Generalized anxiety disorder
OR: Odds ratio
PHQ: Patient health questionnaire
PPR: Prevalence proportion ratio. Interpretation of PPR is similar to relative risk where >1 means increased risk and <1 means decreased risk.
PTSD: Post traumatic stress disorder

3.3.5.2 Diseases/symptoms of the musculoskeletal system and connective tissue as comorbidities/accompanying symptom of widespread pain

Six studies reported findings for comorbid musculoskeletal pain [184,196,203,204,225,226] (Table 3.41). For the comorbidity, one study reported the percentage of osteoarthritis to be 40% and osteoporosis to be 2.2% [184]. Other studies reported the percentage of neck/shoulder/back/arms/legs pain to be 100% [196], and facial pain to be 26% [204]. One study

assessed the types of pain with painDETECT questionnaire where approximately 1/3 or more of patients describe their pain as burning, prickling, spontaneous pain attack, or pressure, and approximately 1/5 of patients described their pain as allodynia, pain evoked by thermal stimuli, or numbness [225]. Shillam et al. on the other hand reported fibromyalgia patients described their pain as pain and stiffness (100% and 99% respectively) [226].

The study by Sipila et al. used prevalence proportion ratio, which was similar to relative risk where >1 means increased risk and <1 means decreased risk. They found that widespread pain increased the risk of getting facial pain by 1.51 [204]. The other study by Schur et al. found fibromyalgia was 5.2 and 10.4 times more likely to have LBP or temporal mandibular joint disorder (TMD) respectively [203] (OR for LBP: 5.2 (4.4-5.9), OR for TMD: 10.4 (5.4-20.1)).

Table 3.41 Musculoskeletal pain comorbidity of fibromyalgia

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
Sipila et al. [204]	Facial pain within widespread pain: 469 (26%)	Compared with general public: Facial pain: PPR 2.51 (2.22-2.83).
Schur et al. [203]	No data	Compared to twins within the Twin Registry without fibromyalgia: Low back pain: 5.2 (4.4-5.9) TMD: 10.4 (5.4-20.1)
Kurtze et al. [196]	Pain in neck/shoulder: 1816 (100%) Back pain: 1816 (100%) Arms/legs pain: 1816 (100%)	No data
Bernatsky et al. [184]	Osteoarthritis: 72 (40%) Osteoporosis: 4 (2.2%)	
Rehm et al. [225]	For painDETECT questionnaire, 29.8% described as burning, 32.6% described as prickling, 20.4% described as allodynia, 39.9% described as spontaneous pain attacks, 24% described as pain evoked by thermal stimuli, 19.8% described as numbness, and 58.3% described as pressure.	
Shillam et al. [226]	Pain: 171 (100%) Stiffness: 170 (99%)	

CI: Confidence interval
OR: Odds ratio
PPR: Prevalence proportion ratio. Interpretation of PPR is similar to relative risk where >1 means increased risk and <1 means decreased risk.

3.3.5.3 Diseases/symptoms of the neurological system as comorbidities/accompanying symptoms of widespread pain

Four studies reported findings for comorbid neurological disorders. Bernatsky et al. included 99 Canadian fibromyalgia participants [184]. Schur et al. included 3982 USA twin participants [203]. Kurtze et al. included 65220 general public and 1816 of them had fibromyalgia [196]. And Shillam et al. included 171 US/Canada fibromyalgia patients [226]) (Table 3.42). They all reported findings on fatigue. The percentage of fatigue ranged from 2.2% to 95%. Fibromyalgia patients are 29.1 times more likely to have chronic fatigue syndrome (OR 29.1 95% CI 26.9-31.5) [203]. This chronic fatigue was based on patients' self-report of doctor's diagnosis.

Shillam et al. [226] reported fibromyalgia patients had sleep related problems ranging from 75% to 93%, memory and concentration problems ranging from 76% to 87%, and other neurological conditions ranged from 53% to 81%.

Schur et al. [203] reported finding for chronic tension type headache. It is found that people who have fibromyalgia was five times more likely to also have tension type headache

Table 3.42 Neurological diseases/symptoms as comorbidities/accompanying symptoms of fibromyalgia

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
Bernatsky et al. [184]	Chronic fatigue syndrome: 4 (2.2%)	No data
Schur et al. [203]	No data	Compared to twins within the Twin Registry without fibromyalgia: The OR and 95% CI after adjusted for age and sex is as following: Chronic fatigue syndrome: 29.1 (26.9-31.5) Chronic tension type headache: 5.0 (4.3-5.7)
Kurtze et al. [196]	Fatigue: 1359 (74.8%)	
Shillam et al. [226]	Restless legs: 98 (57%) Difficulty falling asleep: 128 (75%) Difficulty staying asleep: 146 (85%) Muscle spasms: 138 (81%) Fatigue: 163 (95%)	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
	Nonrefreshing sleep: 159 (93%) Forgetfulness: 149 (87%) Difficulty concentrating: 130 (76%) Falling easily: 99 (58%) Feeling dizzy: 90 (53%)	

CI: Confidence interval
OR: Odds ratio

3.3.5.4 Diseases/symptoms of the digestive system as comorbiditis/accompanying symptoms of widespread pain

Three studies reported findings for comorbid digestive disorders [184,203,226] (Table 3.43). The percentage of irritable bowel syndrome in fibromyalgia patients ranged from 36.1% to 62%. The association between fibromyalgia and irritable bowel syndrome was not significant (OR 1.7 95% CI 0.8-3.9) [203].

Table 3.43 Digestive diseases/symptoms as comorbidity/accompanying symptoms of fibromyalgia

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
Schur et al. [203]	No data	Compared to twins within the Twin Registry without fibromyalgia: *IBS: 1.7 (0.8-3.9)*
Bernatsky et al. [184]	Irritable bowel: 65 (36.1%)	
Shillam et al. [226]	Irritable bowel: 106 (62%)	No data

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
OR: Odds ratio

3.3.5.5 Diseases/symptoms of the genitourinary system as comorbidities/accompanying symptoms of widespread pain

Three studies reported data for comorbid genitourinary disease/symptoms (Table 3.44) [184,226,241]. The percentage of irritable bladder ranged from 1% to 58%.

Table 3.44 Genitourinary diseases/symptoms as comorbidity/accompanying symptoms of fibromyalgia

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
Bernatsky et al. [184]	The comorbidities of the 180 participants are as following: Irritable bladder 1 (1%)	
Shillam et al. [226]	Irritable bladder: 99 (58%)	
Bazzichi et al.[241]	Fibromyalgia only (FM1), Fibromyalgia with lifetime psychiatric comorbidity (FM2) Fibromyalgia with current comorbidity (FM3) ISS score > 30 - indicates sexual dysfunction. 76% of FM3, 64% of FM2, and 43% of FM1 have sexual dysfunction. In total 57% of fibromyalgia have sexual dysfunction. In comparison with healthy controls, there is statistical significant difference between FM patients and health control ($p<0.05$).	No data

CI: Confidence interval
ISS: Index of sexual satisfaction
OR: Odds ratio

3.3.5.6 Diseases/symptoms of circulatory, endocrine systems as comorbidity/accompanying symptoms of widespread pain or other findings

There were two studies reported data for comorbid circulatory disease/symptoms (Appendix 14) [184,226]. The percentage for hypertension/vascular diseases were 10% [184] and for cold hands or bruising easily was 66% each [226].

Only one study, included 99 fibromyalgia participants, reported the percentages for thyroid disease was 5%, for diabetes was 3.3%, and for anaemia/haematological disorders was 3.3% [184].

One study (n=171, USA fibromyalgia participants) reported the percentage of headache amongst fibromyalgia patients was 56% [226]

Two studies reported other findings (Appendix 15) [218,226]. Carbonelle et al. [218] used Fibromyalgia Impact Questionnaire to assess the impact of fibromyalgia on those patients. The author found more than 50% of fibromyalgia patients with symptoms, including pain,

fatigue, stiffness, and did not have a well-rested sleep, rated the impact as severe (50th percentile VAS more than 7/10), and more than 50% of fibromyalgia patients with anxiety and depression rated the impact as moderately severe (50th percentile VAS at least 6.5/10). Shillam et al. [226] used another questionnaire (modified from Memorial Symptom Assessment Scale) and found at least 73% of fibromyalgia patients reported "sensitivity to light or sound", "profuse sweating or feeling hot", and "skin tenderness". Approximately 60% of fibromyalgia patients had "accident prone", "swelling", and "Inability to enjoy life"; and 35% of fibromyalgia patients had pelvic pain.

3.3.6 Summaries for comorbidities/accompanying symptoms of CMP

Summing up the types of comorbidities/accompanying symptoms. This SR included most data on comorbid mental and behavioural disorders (42 studies) and least data on comorbid "Eye and adnexa" and "ear and mastoid process" disorders (9 studies) (Table 3.45). Summaries of the comorbidities of CMP are listed from Table 3.46 to Table 3.48. These three tables only included data if more than one study reported percentage data or ORs on the same comorbidities/accompanying symptoms. There was no reporting of ORs of the same comorbidities/accompanying symptoms for fibromyalgia/widespread pain by more than one study.

Percentage wise, the comorbidity/accompanying symptoms are listed below if the maximal percentage is more than 30%. For chronic SP, the comorbidity/accompanying symptoms included: somatoform disorder (97%), sleeping problem (76%), arthritis (71%), chronic pain (68.6%), GAD (65.7%), alcohol related disorders (64.9%), all kinds of anxiety disorders (45.7%), abuse or dependence of substance (36%), headache (31.9%), and irritable bowel syndrome (30.1%). For arthritis, the comorbidity/accompanying symptoms included: any physical or mental diseases (85.2%), chronic pain (73.4%), back/neck pain (69%), heart disease (54%), obesity/overweight (52.9%), and hypertension (47%). And for widespread pain, the comorbidity/accompanying symptoms included: fatigue (95%), depression/depressiveness (90.9%), anxiety (77.7%), irritable bowel syndrome (62%), and irritable bladder (58%).

For chronic SP and arthritis, they were both associated with headache/migraine, depression, and panic attacks/disorder, hypertension, and heart diseases. Chronic SP and arthritis were both associated with each other. Chronic SP had also been shown to associate with GAD, mood

disorder, alcohol use disorder, digestive ulcer, and other lung diseases (apart from asthma, and tuberculosis); whereas arthritis was associated with PTSD, heart attack, asthma, any chronic pain, any physical disease, and "any mental or physical disorders, pain".

Table 3.45 Number of studies reporting comorbidities and accompanying symptoms

Types of comorbidities	Study
Mental and behavioural disorders/symptoms	42 studies [166,167,175-178,180,182,184-187,189,192,193,196,197,201-204,206-210,212,214,216,217,219,220,222,224-226,228,232-235,241]
Musculoskeletal system and connective tissue disorders	29 studies [166-168,179-181,184,188,190,192,194,196,203,204,207,209,219,220,225-228,230,233,235-237,239,240]
Circulatory disorders	22 studies [166,167,176,180,184,192,194,200,207,209,212,219,220,226-228,230,233,235-237,239]
Endocrine, nutritional and metabolic disorders	20 studies [166,167,176,180,181,184,192,194,200,207,209,219,220,223,227,228,230,233,235,238]
Respiratory disorder	18 studies [166,167,176,180,192,194,200,207,209,212,219,220,227,228,230,233,235,237]
Neurological disorders	18 studies [166,167,180,184,188,190,194,196,203,207,209,220,226,229,230,233,235,240]
Digestive disorder	17 studies [166,167,176,180,184,188,192,203,207,209,219,220,226,230,233,235,240]
Genitourinary disorders	16 studies [180,184,193,200,207,209,219,220,226-228,230,233,235,237,241].
“Signs and abnormal clinical and laboratory findings, not elsewhere classified” (including headache)	9 studies [166,167,190,192,213,226,230,235,240]
“Eye and adnexa” and “ear and mastoid process” disorders	9 studies [166,167,176,180,207,209,233,235,236]

Table 3.46 OR and percentage data of mental and behavioural, digestive, and circulatory, comorbidities/accompanying symptoms of CMP

	Mental and behavioural disorders			**Diseases/symptom of the digestive system**			**Diseases/symptoms of circulatory system**		
CMP type		**OR**	**Percentage**		**OR**	**Percentage**		**OR**	**Percentage**
Chronic SP	Major depression/depression	2.5 - 6.2	11.4% - 64%	Digestive ulcer	3.1-4.0	ND	**Heart disease**	**CF**	3.6% - 6.9%
	GAD	2.54 to 2.6	2% - 65.7%						
	Panic disorder	2.0 to 2.69	2.8% - 8.2%						
	Mood disorder	1.7 - 2.5	ND						
	All anxiety disorders	**CF**	21.6% - 45.7%						
	Abuse or dependence on substances other than alcohol	**CF**	4.1% -36%	Irritable bowel syndrome	ND	1.9% - 30.1%	Hypertension	1.5-2.9	19.3% - 26.6%
	Somatoform disorder	ND	1% - 97%				**Stroke**	**CF**	4.3% - 6.7%
	Alcohol related disorders		2.1% - 64.9%				*Heart attack*	*NA*	ND
	Phobias (including simple phobia, social phobia, and Specific phobia		0% - 25.7%						
	Dysthymia		2% - 23.7%	Digestive ulcer	3.1-4.0	ND			
	Obsessive compulsive disorder		0% - 13.4%						
	PTSD		1% - 7.3%						
	Bipolar I or II		2% - 4.4%						
Arthritis	Depression	1.48-2.82	4.9-24%	*Digestive ulcer / ulcer in stomach or intestine*	*NA*	0.3% – 11%	Heart attack	5.8-8.7	11.8% - 17.1%
	Panic attacks/disorders	2.00-2.09	0% - 0.4%				Heart disease	3.1-4.0	4% - 54%
	PTSD	2.52-3.69	0% - 0.8%				High blood pressure	2.0-2.7	7.3% - 47%
	Dysthymia	**CF**	0.3% - 1.1%						
	Major depression disorder with/without hierarchy		3.9% - 5.7%						
	GAD		2.3% - 3.6%				Stroke	ND	0.7% - 4.2%

	Mental and behavioural disorders			Diseases/symptom of the digestive system			Diseases/symptoms of circulatory system		
CMP type		**OR**	**Percentage**		**OR**	**Percentage**		**OR**	**Percentage**
	Any anxiety		2% - 22.3%						
	Panic disorder with or without agoraphobia		ND						
	Simple phobia		ND						
	Social phobia		ND						
	Specific phobia		3.5% - 7.5%						
	Agoraphobia without panic		ND						
	Any mood disorders		3.9% - 5.7%						
	All mental disorder		10% - 10.5%	Liver diseases	ND	0.9% - 7.4%	Vascular diseases	ND	2% - 25.6%
	Substance use		0.5% - 4.5%						
	Psychiatric diseases/disorder	ND	7.84% - 26.3%						
	Alcohol abuse or dependence	*NA*	0.5% - 4.3%						
	Drug abuse or dependence		0% - 0.2%						
	ADD/ADHD	ND	22.1% - 29%						
Widespread pain	Depression/depressiveness	ND	5% - 90.9%	Irritable bowel syndrome	ND	36.1% - 62%	ND		
	Anxiety	ND	1% - 77.7%						

ADD: Attention deficit disorder
ADHD: Attention deficit hyperactive disorder
CF: Conflicting finding, indicated by bold font
GAD: Generalized anxiety disorder
ND: No data
NA: No association, indicated by italicised font
PTSD: Post traumatic stress disorder

Table 3.47 OR and percentage data of respiratory, “endocrine, nutritional, and metabolic”, “musculoskeletal and connective tissue” comorbidities/accompanying symptoms of CMP

	Diseases/symptoms of the respiratory system			**Endocrine, nutritional and metabolic diseases/symptoms**			**Diseases/symptom of the nervous system**			**Diseases/symptoms of the musculoskeletal system and connective tissue**		
CMP type		**OR**	**Percentage**		**OR**	**Percentage**		**OR**	**Percentage**		**OR**	**Percentage**
Chronic SP	Other lung disease (lung diseases apart from asthma, and tuberculosis)	1.7-2.9	ND	*Diabetes*	*NA*	0.5% - 8.2%	Migraine	1.33 -5.2	12.5% - 25.39%	Arthritis	3.0-7.9	1.5%-71%
	Asthma	**CF**	7.2% - 16.9%				Sleeping problem	ND	12.8% - 76%			
Arthritis	Asthma	3.8-5.0	7.6% - 12.6%	**Diabetes or high blood sugar**	**CF**	0.9% - 22.7%	**Neurological disorders**	**CF**	ND	Chronic back / neck problem	6.5-7.9	6% - 69%
	Tuberculosis	**CF**	0.5 - 3.2%	**Thyroid disease**	**CF**	0.4% - 6.7%	Epilepsy or seizures	ND	0% - 1.5%	Osteoporosis	ND	3.2% - 13.9%
	Other lung disease (apart from asthma and tuberculosis)	**CF**	ND									
	Chronic obstructive pulmonary disease	ND	7% - 14%	Obesity / overweight	ND	16.1% - 54.2%						
Widespread pain	ND						Fatigue	ND	2.2% - 95%	ND		

CF: Conflicting finding, indicated by bold font
ND: No data

NA: No association, indicated by italicised font

Table 3.48 OR and percentage data of "abnormal clinical and laboratory findings, not elsewhere classified", "eye, adnexa, ear and mastoid process", and other comorbidities/accompanying symptoms of CMP

	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified			**Diseases/symptoms of the eye and adnexa and disease/symptom of the ear and mastoid process**			**Other**		
CMP type		**OR**	**Percentage**		**OR**	**Percentage**		**OR**	**Percentage**
Chronic SP	Headache	4.0-7.0	14.6% - 31.9%	Hearing impairment	ND	6.0% - 6.6%	Chronic pain*	3.4-4.8	18.9% - 68.6%
Arthritis	Headache (including frequent/severe headache/migraine)	2.1-4.8	8.7% - 19.8%	*Seasonal allergies*	*NA*	7.8% - 12.4%	Any chronic pain	6.1-6.3	45.2% -73.4%
							Any physical disease	2.3-3.1	ND
							Any mental or physical disorders, pain	4.0-6.2	0% - 85.2%
							Malaria or other parasitic diseases	*NA*	ND
							Renal diseases:	ND	0% - 11.2%
							Cancer	ND	0% - 14.8%
Widespread pain	ND						Irritable bladder	ND	1% - 58%

CF: Conflicting finding, indicated by bold font
ND: No data
NA: No association, indicated by italicised font
*Chronic pain is defined as pain lasted more than six months and may be in any parts of the body ranging from head to toes and including chest, stomach, and pelvic pain.

3.4 Discussion

3.4.1 Summary

The aims of the SR were to identify 1) the types of comorbidities/accompanying symptoms of CMP; 2) the percentages of comorbidities/accompanying symptoms in CMP; and 3) the association between CMP and comorbidity/accompanying symptoms of CMP.

The SR identified that the types of comorbidities/accompanying symptoms of CMP included the mental and behavioural disorders, digestive diseases/symptoms, circulatory disorder/symptoms, respiratory diseases/symptoms, endocrine and metabolic diseases/disorders, nervous system disorders/symptoms, musculoskeletal diseases/disorders, headache, ear and nose symptoms, and other symptoms. The percentage of comorbidities/accompanying symptoms had been summarised in Chapter 3.3.6 Summaries for comorbidities/accompanying symptoms of CMP (p. 124). The most frequently occurred comorbidity/accompanying symptom for chronic SP was somatoform disorder (97%), for arthritis was any mental/physical disorders or pain (85.2%), and for widespread pain was fatigue (95%). Association between CMP and comorbidity/accompanying symptoms was also summarised in Chapter 3.3.6 Summaries for comorbidities/accompanying symptoms of CMP (p. 124). The highly associated comorbidity/accompanying symptoms with chronic SP was arthritis (OR 7.9), with arthritis was heart attack (OR 8.7), and no firm association for widespread pain was found.

The association between CMP and its comorbidities does not reflect any cause-effect relationship. The cause of association included direct/indirect associations between the diseases [110], genetic susceptibility and family history [112], chance alone [110] or unknown of cause [113]. See details in Chapter 2.5.2 What are the causes of comorbidity? (p. 27). The discussion here is limited to the association without speculating on the cause-effect relationship. In this section, the discussion is focused on 1) comparison with other SRs, 2) complexity of CMP comorbidities and its relevance to diagnosis, 3) assessing comorbidities and accompanying symptoms, 4) assessing quality of case control and cohort studies, and 5) the need for urgent attention for CMP management.

3.4.2 Strengths and limitations of this systematic review

The strengths of the SR include:

1) Comprehensiveness. This review searched all conditions of OM and studied all reported comorbidities as well as symptoms.

2) Both the epidemiological and the CMP-specific data were included and the sample sizes were large (total 358559 with a median of 590 and 635);

3) Multiple studies reported findings on the same comorbidity/accompanying symptoms of the same type of CMP were found;

4) Some of the comorbidity assessments, e.g. WHO CIDI, BDI, symptom checklist 90, body mass index, were used by multiple studies which further strengthens the evidence of the comorbidities;

Limitations of this SR include:

1) Only English data were available for analysis. No suitable study was selected from Chinese databases. Key Chinese databases, including CQVIP and Wanfang Data, were searched. Due to the differences in the database interface, the search results came up as either no results from CQVIP, or thousands of non-specific studies from Wangfang Data. This SR did not include studies in Chinese language nor included Chinese databases as part of the search strategy. Data in other languages were excluded;

2) only data from a few countries were reported and available;

3) the outcome measures of the comorbidities were not consistent. This can also affect the consistency of the results; For instance, self reported mental/psychiatric illnesses, BDI, and WHO CIDI.

3.4.3 Comparison with other systematic review on comorbidity and accompanying symptom

There were a few SRs published related to comorbidity and accompanying symptoms of musculoskeletal disorders. Kelly et al. found chronic LBP was associated with greater sleep disturbance, reduced sleep duration and sleep quality, increased time taken to fall asleep, poor

day-time function, and greater sleep dissatisfaction and distress. Inconsistent evidence was found that sleep efficiency and activity were adversely associated with chronic LBP [970].

Shiri et al. substantiated the associations between overweight, long smoking history, high physical activity and a high serum C-reactive protein level with lumbar radicular pain or sciatica [971]. Leboeuf-Yde et al. did not find any study evaluating the dose effect of alcohol on LBP and none of the included studies were prospective in design [972]. Shiri et al. and Leboeur-Yde et al. only focused on Medline searches [971,972] whereas Kelly et al. focused on multi-databases searches [970]. All of those SRs focused on either LBP [970], lumbar radicular pain or sciatica [971], or muscle diseases [973] with their searches up to end of January 2009 (Table 3.49). In comparison, the current review included the latest evidence, with database searches up to 13/05/2015, comprehensive, included both comorbidities and accompanying symptoms and had identified the association between CMP and various disorders, most notably the comorbid mental and behavioural disorders/symptoms (Table 3.45). This SR included none of the studies included in the SRs of Kelly et al. [970] Shiri et al. [971] and Leboeuf-Yde et al [972] since to Kelly et al. specifically searched for and included only chronic LBP reporting sleep problems. Shiri et al. on the other hand searched for back pain including sciatica, radicular pain, and focused on cardiovascular or lifestyle risk factors, including hypertension, without including studies that reported data for hypertension. Furthermore Leboeuf-Yde et al. specifically focused and searched for “alcohol”, “substance abuse”, “life style”, “risk factor”, “epidemiology” and “low back pain”. Their search terms and selection criteria were different from the current SR.

Table 3.49 Comparison with other CMP SRs

Study	Database	Population	Outcome
Kelly et al. [970]	Pubmed, CINAHL Plus, PsychInfo, Pedro, and the Cochrane database of SRs up to January 2009	Chronic LBP	Sleep outcome measures
Shiri et al. [971]	Medline to August 2006	Lumbar radicular pain or sciatica patients	Cardiovascular or lifestyle risk factors and lumbar radicular pain or clinically defined sciatica
Leboeuf-Yde et al. [972]	Medline from 1992 to June 1999	LBP	Consumption of alcohol and LBP.

LBP: Low back pain

3.4.4 The complexity of CMP comorbidities and its relevance to diagnosis

For the associations amongst CMP and comorbidities, it is certain that chronic SP and arthritic pain were associated with other types of pain (OR ranged from 1.33-7.9), including headache, other types of musculoskeletal pain, chronic pain, and other types of diseases (OR ranged from 1.48 – 6.2), including depression, panic disorder, and hypertension. Individually chronic SP and arthritic pain have their own associated comorbidities/accompanying symptoms. Such that alcohol use disorder, digestive ulcer, other lung disease (lung diseases apart from asthma, and tuberculosis) were associated with chronic SP, but not arthritic pain, and heart attack and asthma were associated with arthritic pain, but not chronic SP. Such association show arthritic pain and chronic SP had some similarities and differences. Although the strength of the association might not be as strong as the data informed due to the included studies mainly being reports from USA, and therefore not representing the world population. However, since the confidence intervals of ORs were larger than one, for such association to happen by chance was rare.

These findings also ascertain the associations between CMP and the various comorbidities and add complexity to the understanding of CMP. Those comorbidities could be part of the presentation of CMP, but could also be the results of the treatment. Also, they could interact with each other. In an osteoporosis review, the author used osteoporosis as an example and discussed the depressive comorbidity and how depression and hip fracture increased the risk of each other [974]. The findings were that 14-16% of hip fracture patients developed clinical significant depressive symptoms within six months after hospitalisation from no active depression history and 27% reported depressive reactions amongst the older adults [975]. The daily use of serum serotonin reuptake inhibitor (SSRI) for depression was associated with a 4.0% (95% CI, 1.4-6.6) lower bone mineral density at the hip compared to non-SSRI user [976]. Moreover, the presence of two diseases could relate to a third independent disease, for example psoriasis, cardiovascular disease, and erectile dysfunction [977], bipolar, substance abuse, and psoriasis [977]. Such complex relationship between diseases make diagnosis difficult [978].

Overall, the associations indicated chronic SP and arthritic pain occur together with other diseases/symptoms. It is necessary to look at these CMPs as a syndrome of diseases/symptoms cluster. For example, instead of looking at arthritic pain by itself, the arthritic pain syndrome will encompass arthritic pain, other chronic pain, headache,

depression, panic disorder, heart disease, and asthma. These symptoms and diseases should be viewed together and such approach had been proposed by Hartvigsen et al. [39].

For the included studies on chronic SP and arthritis, there were four studies that reported OR for comorbid arthritis or chronic SP [166-168,192]. Apart from Ijzelenberg et al. [168] who specified the comorbid symptoms as chronic neck pain, chronic shoulder pain, chronic complaints of elbow-wrist-hand pain, and chronic upper extremity complaint, none of the other three studies specified whether or not the arthritis was in the four extremities. Participants of these three studies may have overlapped arthritis and chronic SP where arthritic joint pain could occur within the spine, e.g. hyperplastic vertebrae, or chronic SP may also be considered as arthritis. Subsequently participants selected both the arthritis and chronic SP together and resulted in higher than normal ORs of their association.

For widespread pain, the available data are limited. Multiple studies reported the percentage data for a wide range of accompanying symptoms associated with fibromyalgia and not OR. The accompanying symptoms included depression/depressiveness, anxiety, irritable bowel syndrome, fatigue, and irritable bladder. Those studies have helped the redevelopment of the diagnostic criteria of fibromyalgia. The recently published preliminary new diagnostic criteria for fibromyalgia [979] have included all the above mentioned conditions as well as sleep and cognitive problems. Only the percentage of sleep issues were reported by some of the included studies without OR data. This may be due to the search strategy did not search for fibromyalgia or widespread pain. The new criteria was established due to that the clinical trials reported symptoms in addition to the 1990 American College of Rheumatology criteria for fibromyalgia [980], such as sleep and cognitive problems. Based on the reference list of Wolfe et al. [979], although 10 RCTs were mentioned, their references were not listed [981,982]. And such discrepancy between the current review and the new criteria maybe the current review did not specifically target fibromyalgia but instead focused on CMP.

3.4.5 Assessing comorbidities and accompanying symptoms

Several comorbidity/accompanying symptoms outcome measures were used in the included studies (Table 3.9 to Table 3.11). The most frequently used outcome measures were WHO CIDI, self-reported physical illness, and author -made comorbidity/accompanying symptoms list. For mental disorders, WHO CIDI was consistently used; but for physical illnesses there was heterogeneity in the tools used. Majority of the authors used self-reported physical illnesses

[179,185,190,203,204,210,217,231] including Schur et al. who reported fibromyalgia patients was 29.1 times more likely to develop chronic fatigue where the author obtained the data by asking participants "Has your doctor ever told you that you have chronic fatigue syndrome?" [203], or author made comorbidity/accompanying list [180,213,221,224,232,239,240]. The other different comorbidity questionnaires were each used by single study [187,188,198,202,205,207,211,212,215,218-220,225,229,230,236,241]. Such heterogeneity can lead to problems in integrating findings [983]. As shown in the results section, some authors reported the lumped together results of both liver/kidney diseases [220] and stomach/gall bladder conditions [176]. This made it impossible to separate the data of liver diseases from those of kidney diseases.

3.4.6 Inconsistent results in the included studies

Of the reviewed studies, there were several conflict findings as shown from Table 3.46 to Table 3.48. The possible reasons for such conflict were evaluated and listed in Table 3.50. It was clear that when data were collected from different countries, the results could be different. For example, all anxiety disorders had a conflicting finding between studies where Gureje et al. (Nigeria) reported no association (OR 1.5 (0.9-2.5)) [192], whereas Buist-Bouwman et al. [187] (Netherlands) (OR 1.6 (1.3-2.0)), Tsang et al. [206] (Internationally collaborated study including Colombia, Mexico, USA, Belgium, France, Germany, Italy, Netherlands, Spain, Ukraine, Israel, Lebanon, Nigeria, South Africa, Japan, PRC (Beijing and Shanghai), and New Zealand.) (OR 2.0 (1.8-2.1)), and Von Korff et al. [167] (USA) (OR 2.3 (1.9-2.7)) all showed a positive association between chronic SP and all anxiety disorders. Another possibility is how data were analysed. Two studies presented the same set of data, but data were adjusted differently, resulting in different OR (Appendix 9) [176,202]. This is a concern for SRs as there is no gold standard for the adjustment of ORs.

Table 3.50 Possible explanations for conflicting findings

Possible explanations of conflict finding	Country difference	Same set of data with different kind of adjustment for ORs	Uncertain
chronic SP	All anxiety disorders, stroke, asthma	No conflicting findings	Abuse or dependence on other substances
Arthritis	Dysthymia, major depression disorder alone or with hierarchy, any anxiety, panic disorder with or without agoraphobia, specific phobia, any mood disorders, all mental disorder,	GAD, simple phobia, social phobia, agoraphobia without panic	No conflicting findings

Possible explanations of conflict finding	Country difference	Same set of data with different kind of adjustment for ORs	Uncertain
	substance use, diabetes or high blood sugar, thyroid disease, tuberculosis, other lung disease (apart from asthma and tuberculosis), neurological disorders		

GAD: Generalized anxiety disorder

3.4.7 Assessing quality of case control and cohort studies

NOS was recommended by the Cochrane library and subsequently used in the SR to evaluate the methodological rigour [172]. Currently there are other scales for quality assessment [984,985], but many of their validities and reliabilities have not been established or were designed for interventional studies (e.g. Checklist for Measuring Quality- Downs and Black) and are not suitable for the current SR [985]. The content validity and inter rater reliability of NOS has been established and is valid and a reliable quality appraisal [41].

For the included studies, the NOS scores were graded as unsatisfactory for most of the studies (58 studies). Only14 studies achieved five out of nine on NOS, reaching a satisfactory level. However some authors made the cut off NOS score for low quality studies to be equal to or less than five [986], and this would have graded all the included studies of low quality. Such a low score was due to NOS requiring the control group to be present for five items and requiring the reporting of follow up rate of each group. Many of the included studies did not have a control group and only reported the follow up rate of the whole sample, but not of each individual group. The requirement made some studies unable to score for five items (six scores lost), resulting a low score for many studies.

Another point is the requirement of primary record. Studies described confirmation of diagnosis by specialists (e.g. rheumatologist), without referencing to the primary record (e.g. x-ray, medical/hospital records). Again four studies lost scores on this item [198,199,238,241]. There is no gold standard to evaluate the quality of observational studies [987]. NOS is among the most suitable ones. There is a need to develop a gold standard methodological appraisal instrument for evaluating the quality of observational studies.

Based on the NOS results, the heterogeneity amongst the studies and the lack of suitable scale, caution is advised when interpreting the results.

3.4.8 The need for urgent attention for CMP management

Bair et al. reviewed literatures on depression and pain and found depression and painful conditions frequently coexist [640]. Often patients were referred to a specialist who has expertise in either depression or pain but not to a specialist who was good at both. Primary care practitioners who often encountered the combination of these two conditions often lacked knowledge or expertise to tackle this combination of conditions [640]. A multidisciplinary and personalised pain management is essential to tackle both CMP and comorbidities, and improve both function and QoL [126,988]. Researchers have proposed to have a guideline for each patient, who presents with multi comorbidities, rather than a guideline for each disease [989], but the applicability of current evidence based guidelines for comorbidities is limited as most of them do not provide explicit guidance on treatment for patients with comorbidities [990]. There are so far guidelines for treating comorbidities, but are limited to substance misuse comorbid with mental disorders in Australia [991(p5)992(p1)].

Based on the results of the current SR as well as the literature review on comorbidity (Chapter 2.5 Comorbidities and symptomatology of chronic pain – a new direction of pain management (p. 27)), healthcare practitioners should pay closer attention to the comorbidities when treating CMP. Especially the comorbidities and accompanying symptoms listed from Table 3.46 to Table 3.48 as supported with ORs and prevalence/percentage data. These closer attentions will help health care practitioners to better diagnose, understand the patients' complaints and intervene early in the course of disease progress before the diseases and comorbidities aggravate each other further.

3.5 Conclusion

3.5.1 Implications for practice

Evidence indicates there is a need to view CMPs as CMP syndromes. Chronic musculoskeletal pain syndromes include other bodily pain, mental disorders, and non-pain physical disorders/diseases. When treating CMP syndromes, health care practitioners should be aware of the diseases and accompanying symptoms such syndromes include, and intervene as soon as possible before such patients present with increased numbers of comorbidities and

accompanying symptoms.

3.5.2 Implications for future research

More research is needed into the comorbidities and accompanying symptoms of CMP to better understand their potential cause-result relationship or interaction. Future research should focus on designing high quality studies based on the current methodology quality appraisal (NOS) and may need to focus on updating the diagnostic criteria for CMP including musculoskeletal diseases to reflect the realistic symptom presentation of CMP. Valid tools for observational studies are needed for quality control purpose.

4. Methods of initial CMPQ development

4.1 Introduction

This chapter describes the development and validation process of CMPQ. To develop a questionnaire, a series of steps are involved, including item generation, consultation with experts in the field for face and content validities of the questionnaires, and statistical analysis of validity and reliability. In addition, CMPQ also needed additional statistics such as frequency analysis, chi square tests, factor analysis, cluster analysis, Cochran's Q test, and correlation tests.

There were four stages in the the development and testing of the CMPQ. Figure 4.1 shows the four stages and the work involved. This chapter outlines the method and further details and results are presented in the subsequent four chapters as follows.

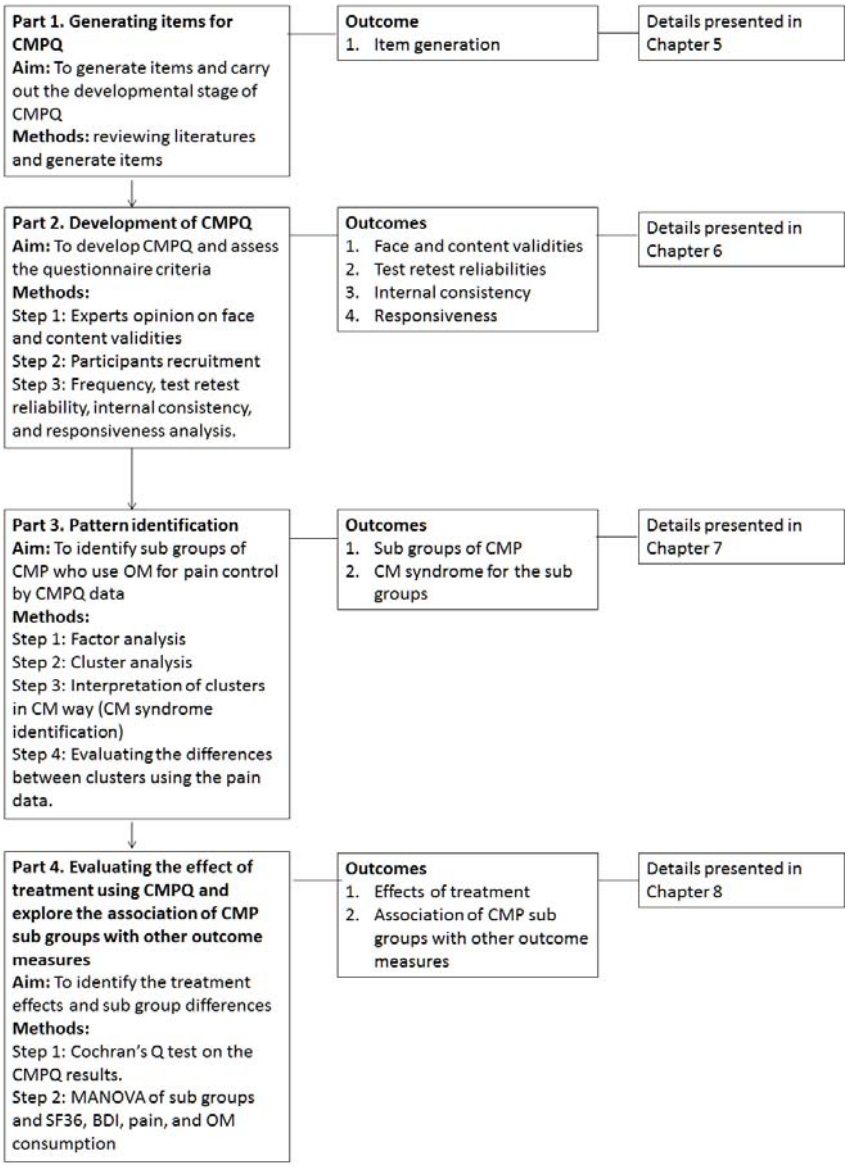
Chapter five, item generation: This chapter detailed the process of how the items were generated for this CMPQ. Relevant literatures were searched and symptoms related to CMP were extracted. The extracted symptoms were grouped into pain regions, pain quality, pain rhythm, pain aggravators, pain alleviators, and accompanying symptoms.

Chapter six, the initial development of CMPQ: This chapter involved experts' discussion on the content and face validities of CMPQ. In addition, CMPQ was tested among EAOM trial participants [1] to evaluate internal consistency, test-retest reliability, and responsiveness which are essential components of questionnaire development.

Chapter seven, the sub grouping of CMP: This chapter included using factor analysis and cluster analysis to sub group the CMP participants. Factor analysis was repeated with different commands in Statistical Package for Social Science (SPSS) several times to identify the factors that were meaningful in CM. Cluster analysis was also repeated with different commands in SPSS to identify the clusters interpretable in CM. Chinese medicine pattern diagnosis was used to interpret the two major clusters. Differences between clusters were also evaluated based on OM consumption, non OM analgesics consumption, average pain intensity, Roland Morris Disability Questionnaire (RMDQ), BDI, and SF36.

Chapter eight, effect of treatments and association with other outcome measures: This chapter

included using CMPQ to evaluate the treatment effect of REA on the symptom presentation. This part also utilised SF36, BDI, and pain diary, which documented pain intensity and OM consumption, to compare the differences in these questionnaires between the two major subgroups of CMP. Results of SF36, BDI, and pain diary were used to identify the differences amongst the two major CMP clusters and the three treatment groups.



BDI: Beck Depression Inventory
CM: Chinese medicine
CMP: Chronic musculoskeletal pain
CMPQ: Chinese medicine pain questionnaire
MANOVA: Multivariate analysis of variance
OM: Opioid medication
SF36: Medical outcome short form health survey 36 items
Figure 4.1 Flow chart of the CMPQ development

Within this chapter, section 4.1 is the introduction which briefly describes the process involved in the CMPQ development and the roadmap of the work completed, section 4.2 outlines the participants involved, the inclusion and exclusion criteria, and the procedures of the EAOM trial in relation to questionnaire completion; section 4.3 describes the assessment of reliability and various forms of validity for questionnaire development; section 4.4 lists the outcome measures used in this developmental stage; section 4.5 describes data collection, and finally section 4.6 outlines the statistical analysis methods used during this developmental stage.

4.2 Initial development of CMPQ

This project was embedded within the EAOM trial [1]. This trial aimed at inducing the release of endorphin, enhancing the opioid binding potential, but did not aim to target the CMP directly [1]. The EAOM trial was approved by Human Research Ethics Committees (HRECs) of Melbourne Health (HREC number: 2009.033), Alfred Health (HREC number: 80.09) and RMIT University (HREC number: 06/09). The EAOM trial participant recruitment and inclusion/exclusion criteria are listed below.

4.2.1 Participant identification

There were several pathways of participant identification and recruitment:

1) patient case records from Pain Services clinic, Royal Melbourne Hospital, Royal Park Campus, and Caulfield Pain Management and Research Centre, Caulfield Hospital, Caulfield were screened,
2) newspaper advertisements for the EAOM trial identified respondents who were screened for the EAOM trial criteria,
3) referrals from general practitioners (GPs) and specialists within Victoria, Australia.

These pathways identified participants for the EAOM trial and CMPQ development.

4.2.2 Inclusion and exclusion criteria

The inclusion criteria for the EAOM trial were as follows:

1) presence of CMP;
2) regularly taking OM for more than three months;
3) willing to reduce their OM usage;

4) 18 years and older;

5) understanding written and spoken English.

The exclusion criteria were:

1) addicted to OM as judged by Pain Medication Questionnaire (PMQ);

2) severely depressed with suicidal tendency as judged by medical doctors and BDI;

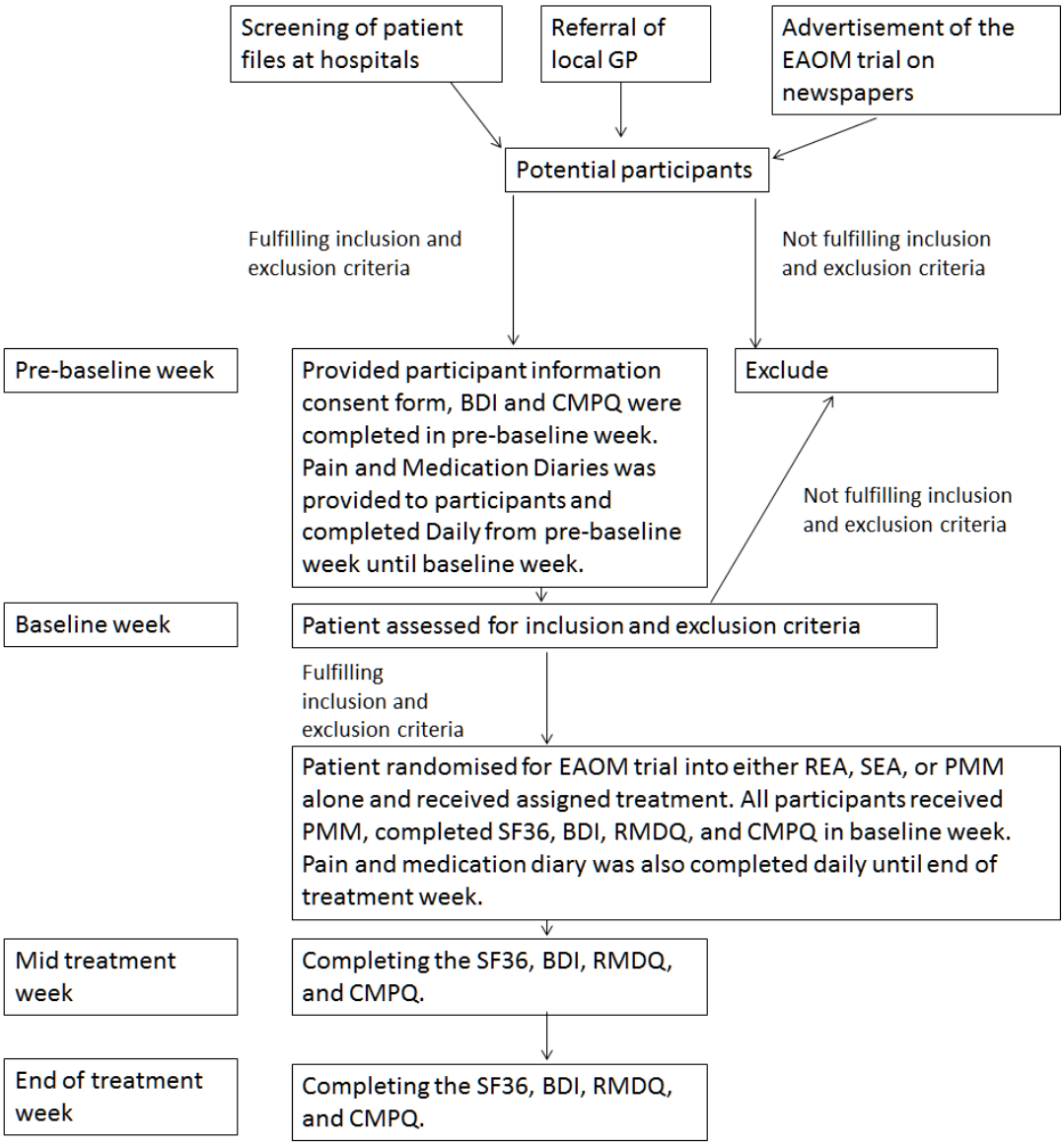
3) abusing drugs, alcohol or having a history of abuse;

4) severe arrhythmia or heart failure, pregnancy or intend to get pregnant, breast feeding women, epilepsy, brain tumour, cancer, haemophilia or wearing cardiac pacemakers.

4.2.3 Procedure of the EAOM trial

Participants were recruited for the EAOM trial if they fulfilled all selection criteria. They were given the participation information consent form and the other questionnaires to complete. Chinese medicine pain questionnaire was one of the questionnaires. Participants completed the questionnaires at one of the following trial centres: either at the Royal Melbourne or Caulfield hospital sites, National Ageing and Research Institute, the Geelong site, the participating CM clinics, or at the Discipline of Chinese medicine, RMIT University, Bundoora, Victoria. Chinese medicine pain questionnaire was handed to participants by the research personnel or by post. The trial procedure is illustrated in Figure 4.2 with details of the questionnaires completed. Treatment phases were divided into four phases – pre-baseline (week one), baseline (week five), mid treatment (week ten), and end of treatment (week 14) weeks. When participants entered baseline week, they were randomised into either real EA (REA), sham EA (SEA), or PMM alone, and completed CMPQ along with BDI, RMDQ, and SF36. Participants completed the same set of questionnaires in mid treatment week and at end of the treatment weeks. In addition, participants also completed daily pain and medication diaries which documented participants' pain intensity and medication usage from pre-baseline week to end of treatment week. For pain diaries, the baseline weeks were defined as from week one to week four and end of treatment weeks was defined as from week 11 to week 14. This was due to participants with CMP having consumed OM for long term. It was necessary to observe their normal OM usage and normal pain level. The average pain and OM consumption over four weeks reflects better the participants' pain and OM consumption.

When comparing the side effects of OM recorded in the pain and medication diary, baseline week was defined as week four.



GP: General practitioner
EAOM trial: Electroacupuncture on opioid consumption by patients with chronic musculoskeletal pain: a randomised controlled trial
BDI: Beck depression inventory
RMDQ: Roland Morris Disability Questionnaire
CMPQ: Chinese medicine pain questionnaire
REA: Real electro acupuncture
SEA: Sham electro acupuncture
PMM: Pain and medication management
SF36: Medical outcome short form health survey36 items
PMM: Pain medication management
PMD: Pain and medication diary
Figure 4.2 Procedure of patient recruitment and administering of questionnaires

4.3 Criteria of questionnaire development

Development of a valid and reliable questionnaire requires fulfilling the questionnaire criteria. These included item generation and reduction, validities and reliabilities, responsiveness, interpretability. They are described in the following sections.

4.3.1 Item generation and reduction

Item generation referrs to generating questionnaire questions that reflect the key concept of the research [993]. Such questions needed to relate to and be accepted by the participants [993]. The source of the items was from texts relevant to the key concept of the research and discussion with experts in the field [993,994]. Item reduction referred to removing items that were redundant, ambiguous, or insensitive to disease progression [995]. Items selected by less than 5% of participants were removed [995]. Chinese medicine pain questionnaire items were generated based on reviewing literatures relevant to CMP from a CM perspective. Details of how the items were generated have been described in Chapter 5 CMPQ item generation (p. 152).

4.3.2 Validities

Validities refer to whether or not a questionnaire was measuring what it was supposed to be measuring [996(p184)993]. Content and face validities were assessed in the CMPQ development.

4.3.2.1 Content validity

Content validity refers to whether the questionnaire items were appropriate and measure what they are supposed to measure [996(p186)997]. Such validity could be achieved by having experts in the field discuss the items through the Delphi method to reach agreement on the included items [996(p186,187)]. The Delphi method is a method used to reach consensus amongst experts [998]. It uses structured surveys to obtain data from the experts [998]. After each round of survey, the data is collected and fed back to the experts [998]. Experts' new responses are influenced by other experts' opinions [998]. Such rounds of survey continue until consensus is reached amongst the experts and generally goes for two to three rounds [999].

In the CMPQ development, content validity was evaluated by assessing if the measurement aim, target population, concept measured, item selection and reduction, and the interpretability of the items of the CMPQ fulfilled the requirement of content validity. Participants in the Delphi process were CM researchers from RMIT Chinese Medicine

Research Group (RCMRG), RMIT University. The requirements for the participating RCMRG researchers were 1) graduated with a minimum of a bachelor degree in CM, 2) having practiced and researched in the CM field for at least three years, 3) be registered with the Chinese medicine registration board, Victoria, and 4) currently working in an educational institution. The participating RCMRG researchers included Dr. Zheng, Zhen (15 years of clinical experience and 13 years of clinical experience), Dr. Wang, Yanyi (4 years clinical and research experience), and Dr. Dong, Lin (over 20 years clinical experience and over 10 years research experience) in 2008. See Chapter 6.3.1 Content validity and face validity (p. 191).

4.3.2.2 Face validity

Face validity refers to the questionnaire appearing to be measuring what it is meant to measure [1000(p82)]. For example, the Oswestry Disability questionnaire achieved face validity when other people looked at it and felt it was measuring the disabilities of LBP. Face validity was assessed by asking the RCMRG researchers whether or not they thought the CMPQ was assessing the symptoms that CMP patients usually have. See Chapter 6.3.1 Content validity and face validity (p.191) for detailed assessment.

4.3.3 Internal consistency

Internal consistency refers to how correlated are the items in the questionnaire [997]. Internal consistency is measured using Cronbach's α [997]. A Cronbach's α value between 0.7-0.95 is considered sufficient [997]. For example, SF36 has questions on physical functioning such as the questions in section three of SF36 "Does your health limit you in these activities". The activities included "vigorous activities", "moderate activities", "lifting or carrying groceries", and "climbing several flights of stairs". A study has shown that SF36 had a high internal consistency for physical functioning (Cronbach's α= 0.90) [1001]. Such an α coefficient indicated the questions were highly correlated.

Internal consistency was assessed in the CMPQ development among the CMP patients who used OM for pain control by using statistical software SPSS. See Chapter 6.3.2 Internal consistency (p. 192).

4.3.4 Reproducibility

Reproducibility is also referred to as test-retest reliability. Test-retest reliability refers to how

similarly a person answered a questionnaire when he/she had been given the test again when there was no change in the person's situation [997]. For example, when a person completed SF36 and scored 70/100 at the first time and then repeated SF36 in three days, during which time there was no change to his health status or other factors relevant to QoL, and he scored 71/100 this second time, the SF36 is said to have test-retest reliability.

Test-retest reliability was assessed in the CMPQ development by comparing the results of CMPQ at pre-baseline week with those at baseline week during the four-week baseline when the participants were informed not to change their usual treatments. See Chapter 6.3.3.1 Agreement (test-retest reliability) (p. 192) for results.

4.3.5 Responsiveness

Responsiveness refers to the ability of the questionnaire to identify clinically important changes before and after an intervention [997]. An example of responsiveness is the changes in BDI. When the change in BDI is five marks, it demonstrates a minimally important clinical difference, a change of 10-19 marks demonstrates a moderate difference, and a change of more than 20 marks demonstrates a large difference [1002].

Responsiveness was assessed in the CMPQ development by comparing the changes in CMPQ between baseline week, mid treatment week, and end of treatment week using the Cochran's Q analysis. The responses of REA and PMM alone were compared. See Chapter 6.3.7 Responsiveness (p. 204) for details.

4.4 Outcome measures

The outcome measures used in this initial CMPQ development included CMPQ, BDI, SF36, and RMDQ, and pain and medication diaries.

Chinese medicine pain questionnaire (Appendix 16) was developed to collect patient data on the symptoms the patient presented with. It focused on musculoskeletal pain with the accompanying non-pain symptoms. It was scored in a dichotomous manner where the symptom either was present or absent. This is the type of data a CM practitioner collects during a patient consultation, either presence of a symptom or absence of a symptom. This questionnaire was divided into six parts, the pain regions, the nature of pain, the rhythm of pain, the aggravators of pain, the alleviators of pain, and the accompanying non-pain

symptoms.

Beck depression inventory (Appendix 17) is a questionnaire used to assess the degree of depression in the patient [1003]. It was developed in 1961[1004], and later developed into BDI I-A and now BDI II [1002,1005]. The current BDI II has 21 questions in relation to the existence and severity of depression [1003]. Each of the questions, except for question 16 and 18, has four choices of answers ranging from no impact of the symptom to severely affected by that symptom [1003,1006]. The total scores were added and the results were interpreted as described in (Table 6.1, p. 185). The psychometric properties of BDI include high internal consistency (Cronbach's α=0.92), high test-retest reliability (coefficient = 0.93), content, construct, and criterion validities, and sensitivity to change where a five point difference indicates a minimum important clinical difference [1006].

Medical outcome short form health survey 36 items (Appendix 18) was developed to evaluate the burden of disease and evaluate the changes between various treatments [1007]. It is a 36 item questionnaire and currently version two has been developed [1007]. These 36 questions can be grouped into eight scales, physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health [1007]. These eight scales can be further summarised into a physical health summary and a mental health summary [1007]. Scoring of SF36 is by a dichotomous response to a six point likert scale. The total score is summed up and organised into the eight scales and further summarised into the two health summaries. The instrument itself has achieved reliability, both internal consistency and test-retest reliability [1007], as well as content, concurrent, criterion, construct, and predictive validities [1007].

Roland Morris disability questionnaire (Appendix 19) was developed in 1983 to assess disabilities associated with LBP [1008]. It contains 24 questions related to the disabilities [1009]. Each question is scored as one if a patient ticks it. The score ranges from 0 to 24 where 0 means no disabilities and 24 means the worst disability. It has good internal consistency (Cronbach's α: 0.84–0.96) [1009]. The intraclass correlation coefficients for test–retest reliability in acute/subacute LBP patients were between 0.86 to 0.93 for one to 42 days test-retest interval [1009]. Roland Morris disability questionnaire also has achieved content, face, and construct validities [1009].

Pain and medication diary (Appendix 20) documented the severity of pain and the use of medication. The questions related to pain were divided into average, highest, and current pain and assessed using VASs. Furthermore there were two questions on the strength/unpleasantness of average pain with a word description next to the numbers for patients to select the number. Lastly there was a question on pain which asked participants to indicate the time of the day participants experienced pain. The medication part included an open ended table asking patients to fill in the types of OM/analgesics they used during the day. Participants were asked to fill in the name of the medication and the dosage of the medication as well as the number of tablets they consumed each time. At the end, there were questions related to the side effects of OMs and pain killers. Participants were asked to rate the severity of the side effects as well as the side effects of acupuncture when they had received EA treatments.

4.5 Data collection

Participants were asked to complete the CMPQ, BDI, SF36, RMDQ, and pain and medication diary (Figure 4.2). These data were collected either at the Royal Melbourne/Caulfield hospitals, Discipline of Chinese medicine, RMIT University, at the participating CM clinics by the research personnel, or by post. The data were entered and double checked by research personnel. Missing data were treated as missing data and no other methods (e.g. intention to treat, or mean score of all participants) were used for CMPQ. Last value carried forward was used for SF36, BDI, and pain and medication diary.

4.6 Statistical analysis

The statistical analysis used for this project included frequency analysis, Chi square test, factor analysis (principal component analysis), cluster analysis (K-means), Cochran's Q test, analysis of variance (ANOVA), and multivariate analysis of variance (MANOVA).

The following is a brief explanation of these statistical methods.

Frequency analysis: Frequency analysis was by summing up the frequency results of all the participants' variables. It was used to provide percentage data on demographic variables and CMPQ items.

Chi square test: Chi square test was used to assess if the distribution of categorical variables were different between the groups or if there was an association between the variables [1010].

Chi square test was used in the project to test if there was a difference between groups in the variables of CMPQ symptoms.

Factor analysis: Factor analysis used statistical software to group variables together into a subset of variables called factors [1011(p628)]. Examples of factors are traits of psychoticism, extraversion and neuroticism where any of the three traits contains a list of psychological symptoms/traits associated with each of them [1012]. Factor analysis and principal component analysis are very similar. Principal component analysis aims to identify the linear components of a set of variables, in other words, its goal is to use the least number of factors to explain the maximal amount of variance whereas factor analysis aims to identify the factors by estimations [1011(p792)]. When applying principal component analysis, it might be that most variables have high factor loadings on the most important factor and small factor loadings on the other variables [1011(p642)]. This would make interpretation of the factors difficult. One method to overcome such a problem is by using factor rotation. Factor rotation refers to rotating the axis of factors so the variables are loaded maximally to the factors [1011(p642)]. One of the factor rotation methods is varimax. Varimax is an orthogonal rotation which aims to maximise the dispersion of the factor loading within the factors [1011(p644)].

In factor analysis, after software groups the variables together, it produces Eigen values, Kaiser–Meyer–Olkin measures (KMOs), and factor loadings. The Eigen value is an indication of the variance of variables in a given factor. KMO is used to assess the sampling adequacy [1011(p647)]. The value of KMO ranges from zero to one where zero means the pattern of correlation in the factors was diffuse and one means the factors were distinct and reliable [1011(p647)]. The interpretation for KMO is: 0.5-0.7 is mediocre, 0.7-0.8 is good, 0.8-0.9 is great and above 0.9 is superb [1011(p647)]. Factor loading is a regression coefficient of a variable to the factor [1011(p786)]. It indicates the relative contribution a variable contributed to a factor. Stevens et al. proposed the following significant factor loading critical values based on sample size (Table 4. 1) [1013].

Table 4. 1 Critical value for correlation coefficient at α=0.01 for a two tailed test.

N	Critical value
50	0.722
80	0.572
100	0.512
140	0.434
180	0.384

N	Critical value
200	0.364
250	0.326
300	0.298
400	0.258
600	0.21
800	0.182
1000	0.162

For each of the resulting factors, it must be interpretable. Otherwise the resulting factors are not meaningful.

Cluster analysis: Cluster analysis refers to using statistical methods to produce meaningful subgroups of individuals [1014(p18)]. Studies have been done using cluster analysis to sub group patients in conditions such as LBP, SP [1015], and upper extremity musculoskeletal disorders [1016]. These three studies used K-means cluster analysis. K-means cluster analysis sub groups observations by reassigning the observations iteratively into a pre-specified number of clusters. It does so until distinctive clusters are found and until the maximum iteration numbers are met [1014(p478)]. K-means cluster analysis can only be used on scaled data but not ordinal data. That is to say when the data is a continuous scale, e.g. zero to ten on VAS, this is suitable for K-means cluster analysis. Whereas if the data is an ordinal scale or a dichotomous data, e.g. zero to five on the pain intensity scale where zero meant no pain, one meant slight pain, two meant just pain, three meant more pain, four meant strong pain, and five meant agonising pain, or a yes/no response where yes meant there was pain and no meant there was no pain, then K-means cluster analysis is not suitable.

After deriving the clusters, these clusters were reviewed by the CM cluster analysis group to diagnose the CM patterns based on the CM eight guiding principles. This group included Dr. Zhen, Zheng; Dr. Yanyi, Wang; Dr. Xinyu (Alan), Hao; Dr. Dawn Lit Wong, and the author.

Cochran's Q test: Cochran's Q test is a test for identifying if there are differences in the change of dichotomous response in groups. That is to say if participants were divided into three groups A, B, and C and they answered yes or no for if they liked to have an X-ray test as part of a routine health check-up. Then, half a year later, they were asked the same question and the results were compared to determine if there were any significant changes in their response.

Association with other outcome measures: Both ANOVA and MANOVA were used to evaluate if there were differences associated with CM patterns and SF36, BDI, OM consumptions, and average pain as well as CM patterns, treatment groups, and the four outcome measures.

ANOVA: Analysis of variance is a statistical test used to find out if there is a difference between three or more groups in the dependent variable [1017]. That is to say if there were three groups A, B, and C and you want to find out if the participant's weights in these three groups differed significantly, you could use ANOVA to find out.

MANOVA: This is ANOVA with several dependent variables. That is to say for the above example, if you were interested in knowing if weight, height, and number of work hours differed significantly amongst the three groups. Then you can use MANOVA for all three variables instead of separate ANOVAs for each individual variable.

4.7 Summary

This chapter listed the key steps in this initial CMPQ development, the roadmap of the project, and the relevant statistical analysis. Next chapter focuses on item generation of CMPQ.

5. CMPQ item generation

5.1 Introduction

In the previous chapter, the methods used for CMPQ development were described. This chapter reports on the first step which was generating the items for a CM questionnaire for application in CMP.

The development of the CM questionnaire incorporated reviewing the literature to generate the items and a delphi expert consultation process for the addition and retention of the items [1018]. In a clinical situation, CM practitioners gather data about the characteristics of pain including pain location, pain rhythm, pain quality, the pain aggravators, the pain alleviators, and the accompanying symptoms. As explained in Chapter 2.6 Chinese medicine (p. 32), these data are used to diagnose a CM pattern. One of the methods of pattern identification is called "CM eight guiding principles". The CM eight guiding principles identify a pattern based on the combination of four categories. These four categories include Yin and Yang, interior and exterior, cold and heat, and deficiency and excess depending on the symptom presentation. For example, the presence of fatigue indicates a deficient pattern whereas the presence of severe pain indicates an excess pattern [1019(p307,531)] and the absence of the symptom may indicate a particular pattern (e.g. excess/deficiency) is not present.

This chapter explains the procedure involved in generating CMPQ items as part of the initial CMPQ development and reports the results for item generation.

5.2 Methods

5.2.1 Literature search

In order to generate the CMPQ items to assess the clinical presentation of CMP from a CM perspective, literature search and experts' opinion were applied. Standard textbooks used in tertiary education and specialised CMP texts in CM were used and searched.

5.2.2 Restriction of language

Languages were limited to Chinese and English.

5.2.3 Search strategies and extracting literature information

Descriptions of all types of CMP were considered. Examples of CMP included LBP (腰痛), Bi syndrome (痹症), arthritis (关节炎), and cervico-spondylopathy (颈椎病). Information related to CMP description, CMP clinical presentation, aggravating and alleviating factors as well as other accompanying non-pain symptoms were extracted.

The criteria for the included textbooks were 1) prescribed textbooks in CM courses offered by tertiary education institutions, or 2) specialised CM book on pain. Exclusion criteria for the items were those items describing acute musculoskeletal pain disease/conditions, such as muscle aches related to influenza.

Symptoms associated with CMP in the included textbooks were extracted. The symptoms may be directly associated with CMP or related to one of the CM patterns of CMP. These symptoms may be related to the location of pain, rhythm of pain, pain quality, alleviating/aggravating factors of pain, accompanying symptoms other than CMP, and gynaecological symptoms. Repetitive items were deleted; and the descriptions of symptoms were rephrased when necessary to avoid medical jargon and make them understandable by a lay person. The resulting items were then categorised into pain regions, pain quality, pain rhythm, pain aggravators, pain alleviators, accompanying non-pain symptoms, and gynaecological symptoms.

5.3 Results

The CMPQ items were generated based on reviewing CMP related conditions/diseases from four texts: 1) the practice of Chinese medicine [1020(p981-1047,1059-1118)], 2) clinical handbook of internal medicine [1021(p308-335)], 3) Chinese internal medicine [132(p706-708,890-895)], 4) Traumatology of Chinese medicine [1022(p963,973,976,984,987,995,996,1002,1005,1007,1012,1014,1017,1019,1023,1032,1034,1042,1045,1047,1051,1054,1062,1069,1078,1094,1097,1107,1108,1116,1131,1136,1158,1168,1171,1172,1176,1177,1306,1325,1536,1538,1541-1548,1554-1557,1567-1570,1574-1576,1579-1581,1583,1584,1586-1588,1631-1635,1642-1644,1650-1651,1652-1653,1654-1656)], and discussion with expert in the field. The expert identified was A/Prof. Zhen Zheng who had a bachelor degree in CM, a PhD degree, and 15 years of CM clinical experience.

Some additional symptoms were added upon discussion with A/Prof. Zhen Zheng. Minor changes were made to the draft questionnaires as a result of discussion. The items “burning

pain", "not known", and an open ended question on "other" pain quality were added in the pain quality domain. Some terms were rephrased e.g. "worse at night" was rephrased as "Worse at night, better during the day". The resultant CMPQ included 187 items. Dichotomous data format was used, which meant the symptom was either present/absent to be consistent with clinical practice.

5.3.1 Composition of the questionnaire

CMPQ items were grouped into the six domains. These six domains were pain regions, pain quality, pain rhythm, pain aggravator, pain alleviator, and accompanying symptoms.

1) Pain regions were arranged and categorised according to the anatomical body regions modified based on International Association for the Study of Pain coding for chronic pain [1023](p3). These categories included a) head, neck & shoulder (seven items), b) upper limbs (six items), c) lower limbs (nine items), d) front of the body trunk (five items)), and e) back of the body trunk (five items). There were a total of 32 items. The exact items are listed in Table 5.1.

Table 5.1 Pain region items generated from literature search

Pain regions	Item
Head, Neck & Shoulder	Frontal head
	Sides of the head
	Back of the head
	Vertex
	Neck
	Shoulder
	Shoulder blades
Upper limbs	Upper arm
	Elbow
	Forearm
	Wrist
	Hand
	Fingers
Lower limbs	Hip
	Thigh
	Knee
	Front of the leg
	Calf
	Ankle
	Heel
	Sole
	Toes
Front of the body trunk	Chest

Pain regions	Item
	Stomach
	Abdomen
	Groin
	Side of the body
Back of the body trunk	Between shoulder blades
	Middle Back
	Lower back
	Sacrum
	Buttocks

2) Pain quality and pain rhythm items are listed in Table 5.2. There are 14 items for pain quality with the last item being an open ended question for participants to describe if they could not find a suitable description. There are12 items for pain rhythm with the last item being an open ended question for participants to describe if they could not find a suitable description.

Table 5.2 Pain quality and pain rhythm items generated from literature review

Item category	Items
Pain quality	Cold
	Pulling
	Distending
	Fixed location
	Moving from one spot to another
	Sharp
	Pricking
	Numbness
	Dull
	Dull pain with weakness
	Hot
	Burning
	Not known
	Other (please specify)
Pain rhythm	All the time
	Recurrent
	Fluctuate
	Worse during the day, better at night
	Worse at night, better during the day
	Worse when first get up
	Worse at the end of the day
	Worse in the morning
	Worse at lunch time
	Worse in the afternoon
	Not known
	Other (please specify)

Italicised items mean additional items upon discussion with A/Prof. Zhen Zheng.

3) Pain aggravators were arranged according to the types of aggravators (Table 5.3): a) environmental changes (five items); b) exercise or sports (10 items); c) physiological and psychological changes (five items), d) others (four items), and e) female menstrual cycle (three items). There were two additional items not belonging to the above groups. One was “not known” and the other one was “others (please specify)”. “Others (please specify)” was an open ended question for participants to describe the aggravators if they were not listed in this section. In total there were 29 items.

Table 5.3 Pain aggravators items generated from literature review

Types of aggravators	Item
Environmental changes	Cold weather
	Wet weather
	Windy days
	Weather change
	Hot weather
Exercise of sports	*Standing*
	Walking
	Lying-down
	Physical work
	Sitting
	Lifting
	Bending
	Any movement
	Going up/down stairs
	Driving
Physiological and psychological changes	*After eating*
	Being hungry
	Bad night sleep
	Stress
	Being emotional
Others	Pressure on the area
	Sex
	Everything
	Household chores
	Not known
	Others (Please specify)
Female menstrual cycle	*Before period*
	During period
	After period

Italicised items mean additional items upon discussion with A/Prof. Zhen Zheng.

4) Pain alleviators items were arranged similarly to pain aggravators. They were also grouped into a) environmental changes (eight items); b) exercise or sports (nine items); c) physiological and psychological changes (five items); d) others (14 items), and e) female menstrual cycle (three items). There were two additional items not belonging to the above groups. One was “not known”, and the other one was “others (please specify)”. “Others (please specify)” was an open ended question for participants to describe the alleviators if they were not listed in this section. The items are slightly different from the pain aggravators and are listed in Table 5.4. In total, there were 41 pain alleviator items.

Table 5.4 Pain alleviators items generated from literature review

Types of alleviators	Items
Environmental changes	*Cold weather*
	Wet weather
	Windy days
	Hot packs
	Cold packs
	Hot weather
	Warm/hot bath
	Warm/hot shower
Exercise or sport	*Standing*
	Walking
	Lying-down
	Sitting
	Gentle massage
	Gentle exercise
	Any movement
	Resting
	Driving
Physiological and psychological changes	*Eating*
	Being hungry
	Deep breathing
	Belching
	Bowel movement
Others	*Pain killer*
	Pressure on the pain area
	Keeping my mind off pain
	Being with other people
	Alcohol
	Reading
	Sleep
	Working
	Watching TV
	Keeping busy
	Sex
	Everything
	Household chores
	Nothing
	Not known
	Other (please specify)
Female menstrual cycle	*Before period*
	During period
	After period

Italicised items mean additional items upon discussion with A/Prof. Zhen Zheng.

5) The accompanying symptoms (Table 5.5). The accompanying symptoms were divided into two groups. They were the accompanying symptoms (46 items) and gynaecological related symptoms (13 items). In both categories, the last item "Others (please specify)" was an open ended question for participants to describe other accompanying symptoms/gynaecological symptoms if they were not listed in this section. In total there were 59 items in this category.

Table 5.5 Accompanying symptom items generated from literature review

Item category	Items
Accompanying symptoms	Swollen joints
	Red and hot joints
	Cold joints
	Limited movement
	Distention sensation in the abdomen
	Indigestion
	Heavy sensation in the body
	Cold hands and feet
	Cold lower back or knees
	Feeling cold easily
	Feeling hot easily
	Insomnia
	Night sweating
	Irritable
	Dry or sore throat
	Flushed face
	Hot palms
	Thirsty
	Watery diarrhoea
	Mushy stools
	Dry stools
	Constipation
	Dry skin
	Leak when sneezing or cough
	Frequent urination at night
	Frequent urination
	Poor concentration
	Poor memory
	Low libido
	Poor appetite
	Feeling tired easily
	Sigh often
	Need deep breath
	Short of breath
	Sweat upon mild activities
	Catch cold easily
	Abdominal distention
	Stuffiness in the chest

	Feeling nervous easily
	Feeling depressed
	Reflux
	Belching
	Nausea
	Dizziness
	Skin itch
	Others (please specify)
Gynaecological symptoms	*Abdominal pain during or before periods*
	Low back pain during or before periods
	Dark blood
	Light blood (pink)
	Bleeding with clots
	Excessive bleeding
	Light bleeding
	Delayed periods
	Early periods
	Irregular periods
	Excessive watery discharge
	Yellow discharge
	Other (please specify)

Italicised items mean additional items upon discussion with Dr. Zhen Zheng.

Overall there were 187 items in CMPQ. Table 5.6 lists the number of items in each of the CMPQ categories. The accompanying symptoms category has the highest number of items and pain rhythm category has the least number of items.

Table 5.6 Number of items in the CMPQ

Category	**Main items**	**Open ended question**	**Female related questions**	**Total**
Pain region	32	0	0	32
Pain quality	13	1	0	14
Pain rhythm	11	1	0	12
Pain aggravators	25	1	3	29
Pain alleviators	37	1	3	41
Accompanying symptoms	45	2	12	59
Total	163	6	18	187

5.4 Discussion

This chapter listed the steps and results of how CMPQ items were generated. The generated items were grouped into pain regions, pain quality, pain rhythm, pain aggravators, pain

alleviators, and accompanying symptoms. The included accompanying symptoms covered a wide range of symptoms necessary for CM pattern identification. This feature was distinctive to CM in comparison to Western medicine.

The anatomical region was incorporated into the CMPQ and coding of chronic pain from IASP was used. In CM, apart from the lower back region, which indicated a CM kidney involvement; other regions of the body were not relevant in CM pattern diagnosis.

For pain quality, the McGill pain questionnaire [1024] is available. It lists many types of pain sensations such as boring, drilling, scalding, and smarting. Some of these pain sensations could be understood from CM perspective, e.g. sharp, and pricking (Table 5.7), whereas some were not explainable in CM point of view, e.g. smarting, boring, and drilling. Consequently McGill pain questionnaire was not incorporated within CMPQ.

Different kinds of pain rhythm could mean different patterns such as pain worse in the morning means dampness retention and pain that fluctuates means Qi stagnation. So these were included in the CMPQ (Table 5.7).

Table 5.7 Pain quality and rhythm and their CM eight guiding principles explanation

Item category	Items	CM eight guiding principles								
		Yin	**Yang**	**Exterior**	**Interior**	**Cold**	**Heat**	**Deficient**	**Excess**	**Comments**
Pain quality	Cold				x	x				
	Pulling				x	x			x	
	Distending				x				x	Qi stagnation
	Fixed location				x				x	Blood stagnation
	Moving from one spot to another			x	x				x	This symptom can indicate **interior** pattern, if it accompanies with dull ache; or **exterior** pattern if accompanies with numbness, stiffness, or spasm.
	Sharp				x				x	Blood stagnation
	Pricking				x				x	Blood stagnation
	Numbness				x			x	x	This symptom can indicate **deficiency** pattern if there is accompanying weakness in the extremity, withered and lustreless complexion, shortness of breath, palpitation, dizziness and vertigo, pale nails and lips; or **excess** pattern if there is accompanying symptom aggravation by cold weather, aversion to cold, cold extremities, sore and heaviness in the lumbar or knee, pins and needles sensation, dull and distending sensation, dark complexion, purple lips, tremor of the extremities, dizziness, irritability, short temper, insomnia with excessive dreams, itchiness, vertigo, heaviness in the shoulder and back, or nausea, copious phlegm, heaviness and pain in the limbs, not very thirsty, both feet prefers to step on cool area, heaviness sensation, nausea, dizziness, or chest stuffiness.

Item category	Items	CM eight guiding principles								
		Yin	**Yang**	**Exterior**	**Interior**	**Cold**	**Heat**	**Deficient**	**Excess**	**Comments**
	Dull				x				x	Qi stagnation
	Dull pain with weakness				x			x		Qi stagnation
	Hot				x		x			
	Burning				x		x			
	Not known									
Pain rhythm	*All the time*									
	Recurrent				x				x	Dampness retention
	Fluctuate				x				x	Qi stagnation
	Worse during the day, better at night		x		x			x		
	Worse at night, better during the day	x			x			x		
	Worse when first get up				x				x	Dampness retention
	Worse at the end of the day				x			x		Qi deficiency
	Worse in the morning				x				x	Dampness retention
	Worse at lunch time									
	Worse in the afternoon									
	Not known									

*Pain character in italicised font indicates no possible CM explanation.
Information extracted from Chinese medicine diagnosis [38(p50-53)], and Differential diagnosis of symptom in Chinese medicine [1025(p223-225)].

Pain aggravators and alleviators could have a close link to the CM pattern such as worse in wet weather means dampness retention and worse in the cold weather means cold retention (Table 5.8 and Table 5.9). For pain aggravated by physical work such as lifting, bending, going up/down stairs, these indicate Qi deficiency as Qi is considered a source of nutrients that nourishes the muscle, tendon, bone and skin [130] whereas pain aggravated by lying down and sitting are a symptom related to dampness retention [38(p179)] pain aggravated by stress/being emotional is due to stagnation of Qi, and pain aggravated by pressure on the area indicated excess. For pain alleviators, they were opposite to the pain aggravators in many aspects such as pain alleviated by hot weather indicates cold retention, pain alleviated by walking indicated dampness retention (excess as oppose to Qi deficiency in the pain aggravators), and pain alleviated by pressure on the area indicated deficiency.

Table 5.8 Pain aggravators and their CM eight guiding principles explanation

Pain aggravator categories	**Items**	**CM eight guiding principles**								
		Yin	**Yang**	**Exterior**	**Interior**	**Cold**	**Heat**	**Deficient**	**Excess**	**Comments**
Environmental changes	Cold weather					x			x	
	Wet weather				x				x	Dampness retention
	Windy days			x						
	Weather change				x				x	Dampness retention
	Hot weather				x		x		x	
Exercise of sports	*Standing*									
	Walking				x			x		Qi deficiency
	Lying-down				x				x	Dampness retention
	Physical work				x			x		Qi deficiency
	Sitting				x				x	Dampness retention
	Lifting				x			x		Qi deficiency
	Bending				x			x		Qi deficiency
	Any movement				x			x		Qi deficiency
	Going up/down stairs				x			x		Qi deficiency

Pain aggravator categories	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
	Driving									
Physiological and psychological changes	After eating				x				x	Food retention
	Being hungry									
	Bad night sleep	x			x			x		
	Stress				x				x	CM liver Qi stagnation
	Being emotional				x				x	Qi stagnation
Others	Pressure on the area				x				x	
	Sex				x			x		
	Everything									
	Household chores				x			x		Qi deficiency
	Not known									
Female menstrual cycle	*Before period*									
	During period									
	After period									

*Pain character in italicised font indicates no possible CM explanation.
Information extracted from Chinese medicine diagnosis [38(p50-53,81-100)] Chinese medicine internal medicine [134(p135)]Principle of Chinese medicine[133(p37,95,96)]

Table 5.9 Pain alleviators and their CM eight guiding principles explanation

Pain alleviator categories	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
Environmental changes	*Cold weather*									
	Wet weather									
	Windy days									
	Hot packs				x	x		x	x	This symptom may indicate **excess** pattern if there is accompanying

Pain alleviator categories	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										cold limbs, abdominal pain and refused to be touched; or **deficiency** pattern if there is accompanying cold limbs, abdominal pain preferring to be touched, loose stool.
	Cold packs				x		x	x	x	This symptom may indicate **excess** pattern if there is accompanying fever with preference of cold temperature, thirst with preference of cold drinks, red face and eyes, irritability; or **deficiency** pattern if there is accompanying malar flush, emaciation, tidal fever, night sweating, heat in the chest/palm/soles, dry mouth and thirst.
	Hot weather				x	x		x	x	Same as hot packs
	Warm/hot bath				x	x		x	x	
	Warm/hot shower				x	x		x	x	
Exercise or sport	Standing									
	Walking				x				x	Dampness retention
	Lying-down				x			x		
	Sitting				x			x		
	Gentle massage							x		
	Gentle exercise								x	Dampness retention
	Any movement								x	Dampness retention
	Resting							x		Qi deficiency

Pain alleviator categories	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
	Driving									
Physiological and psychological changes	*Eating*									
	Being hungry								x	Food retention
	Deep breathing									
	Belching									
	Bowel movement				x				x	
Others	*Pain killer*									
	Pressure on the pain area				x			x		
	Keeping my mind off pain									
	Being with other people									
	Alcohol				x	x				Interior cold retention
	Reading									
	Sleep	x			x			x		
	Working				x				x	Dampness retention
	Watching TV									
	Keeping busy									
	Sex									
	Everything									
	Household chores				x				x	Dampness retention
	Nothing									
	Not known									
Female menstrual cycle	*Before period*									
	During period									
	After period									

*Pain character in italicised font indicates no possible CM explanation.
Information extracted from Chinese medicine diagnosis [38(p50-53,81-100)]

For other symptoms (Table 5.10), they also have CM interpretations such as “red and hot joints” as well as “swollen joints” indicate heat retention, whereas "leaking urine when sneezing or coughing", "frequent urination at night", "frequent urination", "feeling tired easily", "need a deep breath", "short of breath", and "sweat upon mild activities" all indicate Qi deficiency.

Table 5.10 Accompanying symptoms and their CM eight guiding principles explanation

Item category	**Items**	**CM eight guiding principles**								
		Yin	**Yang**	**Exterior**	**Interior**	**Cold**	**Heat**	**Deficient**	**Excess**	**Comments**
Accompanying symptoms	Swollen joints				x		x		x	
	Red and hot joints				x		x		x	
	Cold joints		x		x			x		
	Limited movement									
	Distention sensation in the abdomen				x				x	Dampness retention
	Indigestion				x			x		CM spleen Qi deficiency
	Heavy sensation in the body				x				x	Dampness retention
	Cold hands and feet		x		x			x		CM spleen Yang deficiency
	Cold lower back or knees		x		x			x		CM kidney Yang deficiency
	Feeling cold easily		x		x			x		
	Feeling hot	x			x			x		

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
	easily									
	Insomnia	x			x		x	x	x	This symptom may indicate **Yin deficiency** pattern if there is accompanying night sweating, emaciation, feverish sensation in chest/palm/soles; or **excessive heat** pattern if there is accompanying constipation, red eyes and/or face, thirst with preference of cold drink, and irritability.
	Night sweating	x			x			x		
	Irritable				x		x		x	
	Dry or sore throat	x		x	x		x	x	x	This symptom may indicate **exterior/interior/Yin deficiency/excessive heat** patterns. If this is **exterior heat** pattern, patient may also have fever, slight chill, and cough with yellow phlegm. If this is **interior excessive** heat pattern, patient may also have coarse breathing, high grade fever, thirst, irritability, and cough with thick yellow phlegm. If this is **Yin deficiency/deficient heat** pattern, patient may accompany with steaming bone sensation, night sweating, heat in chest/palms/soles, dizziness and vertigo.
	Flushed face	x			x			x		
	Hot palms	x			x			x		
	Thirsty				x		x	x	x	This symptom may indicate **deficient/excessive heat** pattern depending on

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										if patient present with symptoms of **interior excessive heat** pattern or **Yin deficient** pattern as described in "Dry or sore throat".
	Watery diarrhoea		x		x			x		
	Mushy stools				x			x		
	Dry stools	x			x		x	x	x	This symptom may indicate **interior deficient/excessive/cold/heat** pattern. The **interior excess** pattern includes excessive heat pattern, Qi stagnation pattern, and cold retention pattern. Their symptoms include dry stool, scanty and red urine, red face with feverish sensation, abdominal distention/pain, dry mouth, foul breath; frequent hiccup, fullness and distention sensation in the chest and hypochondriac region, distending pain in the abdomen, poor appetite; clear profuse urine, pale complexion, cold extremity, prefers warmth and dislike scold, cold pain in the abdomen, cold and ache in the lumbar spine. The **interior deficiency** pattern includes Qi deficiency pattern and blood deficiency pattern. Their symptoms include shortness of breath after cleaning bowel, fatigue after cleaning bowel, stool not dry/hard, pale complexion, lassitude; pale complexion, dizziness and vertigo, palpitation.
	Constipation	x			x		x	x	x	
	Dry skin	x			x			x		
	Leak when sneezing or				x			x		Qi deficiency

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
	cough									
	Frequent urination at night				x			x		Qi deficiency
	Frequent urination				x			x		Qi deficiency
	Poor concentration				x			x		
	Poor memory	x			x			x		
	Low libido		x		x			x		
	Poor appetite				x			x		
	Feeling tired easily				x			x		Qi deficiency
	Sigh often				x			x		Deficiency of CM lung
	Need deep breath				x			x		Qi deficiency
	Short of breath				x			x		Qi deficiency
	Sweat upon mild activities				x			x		Qi deficiency
	Catch cold easily				x			x		Qi deficiency
	Abdominal Distention				x	x	x	x	x	This symptom may indicate **interior/cold/heat/deficient/heat** pattern. **Interior cold excess/deficient** patterns may include cold dampness obstruction in middle Jiao pattern, CM spleen and CM stomach deficient cold pattern. Their symptoms include abdominal distention, pressing does not alleviate the distention, poor appetite, nausea

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										and vomiting, heaviness in the head and body, diarrhoea, or pain in the epigastrium and abdomen, thirsty without preference to drink, or yellowing in the body and eyes, females may have excessive vaginal discharge; intermittent abdominal distention with varying severity, prefers heat and being pressed, symptom alleviated by hot drinks/food, fatigue, poor appetite. **Interior heat excess** patterns may include damp heat retention pattern, excessive heat accumulation in CM stomach and CM intestine. Their symptoms include abdominal distention, nausea and vomiting, chest stuffiness, thirst without preference to drink, sweats often, watery diarrhoea, scanty and red urine; abdominal pain may be hard or occurs around the navel, constipation, streaming sweating, tidal fever, manic speech. **Interior excess** pattern includes food retention in the CM spleen and CM stomach. Its symptoms includes abdominal distention, hiccup, acid regurgitation, or dislikes the smell of food, or diarrhoea with a foul smell like a rotten egg.
	Stuffiness in the chest				x	x			x	
	Feeling nervous easily				x			x		Deficiency of CM kidney

Item category	Items	CM eight guiding principles								
		Yin	**Yang**	**Exterior**	**Interior**	**Cold**	**Heat**	**Deficient**	**Excess**	**Comments**
	Feeling depressed	x	x		x		x	x		This symptom may indicate **Yang/Yin/interior/excess/deficient/heat** pattern. **Excess** patterns may have Qi stagnation pattern, Qi stagnation turning into fire pattern, and Qi stagnation with phlegm retention pattern. Their symptoms include depression, emotional restlessness, sigh often, distension pain at chest and hypochondriac region, pain that moves around, stuffiness in epigastrium, hiccup, abdominal distension with poor appetite, vomiting, females may have irregular menstruation; irritability and easy to get angry, stuffy chest with distension sensation at the hypochondriac region, acid regurgitation, dry mouth, bitter taste in the tongue, constipation, or headache, red eyes, tinnitus; globus sensation, stuffiness in the chest, or accompanied with pain at the hypochondriac region. **Deficient** patterns may include depression that damages the spirit, deficiency of both CM heart and CM spleen, Yin deficiency with excessive fire. Their symptoms include absent minded, distraught, grievous and cry often, yawn often; over thinking and over worrying, palpitation and timidity, poor sleep and forgetful, lustreless complexion, dizziness and fatigue, poor appetite; vertigo, palpitation, poor sleep, irritability, or nocturnal emission with low back soreness, females may have irregular menstruation.

Item category	Items	CM eight guiding principles								
		Yin	**Yang**	**Exterior**	**Interior**	**Cold**	**Heat**	**Deficient**	**Excess**	**Comments**
	Reflux				x	x		x		Deficient cold in CM spleen and CM stomach.
	Belching	x	x		x	x	x	x	x	This symptom may indicate **Yang/Yin/interior/excess/deficient/heat/cold** pattern. **Excessive cold** pattern may have belching aggravated by cold property food/environment and alleviated by hot/warm property food/environment, and poor appetite. **Excessive heat** pattern may have symptoms of loud belching, foul breath, irritability, prefers cold drinks, scanty red urine, and constipation. **Interior Yang deficiency** pattern may have feeble hiccup sound, shortness of breath, pale complexion, cold limbs, poor appetite, and fatigue. **Interior Yin deficiency** pattern may have rapid discrete hiccup sound, dry mouth or throat, irritable, and restless.
	Nausea	x			x	x		x	x	This symptom maybe indicate **interior excess/interior deficiency** pattern. Food retention (**interior excess**) pattern may have vomiting with acid regurgitation, abdominal distention, hiccup, poor appetite, nausea aggravated by food consumption and alleviated by vomiting, foul smell stool or diarrhoea, or constipation.

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										Phlegm retention (**interior excess**) pattern may have vomiting out water and saliva, epigastrium distention, poor appetite, vertigo, and palpitation. CM liver Qi attacks CM stomach (**interior excess**) pattern may have vomiting, acid regurgitation, frequent hiccup, distending pain in the chest and hypochondriac region. Deficient cold in CM spleen and CM stomach (**interior deficiency**) pattern may have easily vomiting, pale complexion, fatigue, weakness, dry mouth and does not wish to drink, cold extremities, and loose stools. Deficient CM stomach Yin (**interior deficiency**) pattern may have recurrent nausea and vomiting, dry retching, dry mouth and throat, poor appetite.
	Dizziness	x	x		x			x	x	This symptom may indicate **Yin/Yang/deficient/excess** patterns. **Excess** pattern may have CM liver Yang upsurge pattern, and phlegm turbidity obstruct the middle Jiao pattern. The accompanying symptoms may have tinnitus, headache with a distending sensation, aggravated by irritation and anger, malar flush, easily irritated and grumpy, poor sleep with dreams, bitter taste in the mouth; headache with mental cloudiness, chest stuffiness, nausea, poor appetite,

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										somnolence. **Deficiency** pattern may have Qi and blood deficiency pattern, and CM kidney essence deficiency pattern. The accompanying symptoms include dizziness aggravated by movement, physical labour, and fatigue. Pale complexion/lips/nails, lustreless hair, palpitation, somnolence, fatigue, poor appetite; fatigue, somnolence with dreaminess, forgetful, sore and weak knee and low back, nocturnal emission, tinnitus, feverish sensation in the chest/palms/soles, cold extremities, cold body.
	Skin itch			x	x		x	x	x	This symptom may indicate **exterior/interior/heat/deficient/excess** patterns. The **excess** patterns include both the **exterior and interior** patterns. These patterns include wind pattern, dampness pattern, and heat pattern. The wind pattern symptoms include itchiness that moves around, whole body feels itch, patient may scratch to bleed, the skin is normally dry. The dampness pattern symptoms include blisters, erosions, pustules, ulceration, or is infectious. The heat pattern symptoms include papules, erythema with feverish sensation, blisters, scabs, and are often not infectious.

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										The **deficiency** pattern includes the **interior deficiency** pattern which is blood deficiency pattern. The symptoms include thickened skin, dry, itch, skin scales off, oozes out fluid, rarely there is erosion.
Gynaecological symptoms	Abdominal pain during or before period periods				x				x	
	Low back pain during or before periods							x	x	This symptom may indicate **excess** or **deficient** pattern. The **excess** pattern includes patterns of Qi and blood stagnation, cold dampness retention, and downpour of damp heat. Their symptoms include distending abdominal pain before period and refused to be touched, distending breast pain, scanty menstrual blood, purple dark blood with spots, period pain that is alleviated after the excretion of menstrual blood clots and is relieved when the menstruation finishes; cold abdominal pain before or during period, pain alleviated by heat and aggravated by pressing, scanty menstrual blood with dark black colour and clots, aversion to cold and body ache; abdominal pain before period with feverish sensation, or accompanies with low back distending pain, or abdominal pain aggravated by period, low grade fever, dark red thick menstrual blood with clots, thick yellow vaginal discharge,

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										short yellow urine; The **deficiency** pattern includes pattern of Yang deficiency with cold retention, deficiency of Qi and blood, CM liver and CM kidney deficiency. The accompanying symptoms include cold abdominal pain during or after menstruation with preference to be pressed, pain is alleviated by heat, scanty menstrual blood, dark pale in colour, sore low back and legs, clear profuse urine; dull abdominal pain during or after period, or empty and falling sensation of abdomen and genitalia, prefers to be touched and rubbed in the abdomen, scanty menstruation with pale colour and thin in quality, lassitude, weakness, or pale complexion, poor appetite, diarrhoea; continuous dull ache in abdomen 1 or 2 days after menstruation, sore loin, scanty and thin dark pale menstrual blood, tidal fever, tinnitus.
	Dark blood				x	x			x	
	Light blood (pink)				x			x		Qi deficiency
	Bleeding with clots				x	x			x	
	Excessive bleeding				x		x	x	x	This symptom may indicate **interior excess** or **interior deficiency** patterns. **Interior excess** pattern includes the patterns of heat in the blood, and blood stasis. Their symptoms include excessive bright/deep red thick menstrual blood, or accompanies with

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										small blood clots, irritability, thirst, yellow urine, constipation; excessive purple black menstrual blood that is difficult to clear/stop, blood clots, abdominal pain refused to be pressed. **Interior deficiency** pattern includes Qi deficiency pattern. The accompanying symptoms include excessive amount of thin pale red menstrual blood, pale complexion, shortness of breath, and reluctant to talk, weak limbs, or empty falling sensation in the tummy, or heart palpitation.
	Light bleeding				x			x	x	This symptom may indicate **interior excess** or **interior deficiency** patterns. The pattern of **interior excess** includes patterns of blood stasis, and phlegm dampness. Their accompanying symptoms include dark purple scanty menstrual blood with clots, distending abdominal pain and refused to be touched, the distending pain is alleviated after the excretion of menstrual blood clots; or scanty pale red thick and greasy like phlegm menstrual blood, overweight, chest stuffiness, nausea, vomiting, greasy and sticky vaginal discharge. The pattern of **interior deficiency** includes patterns of blood deficiency, and CM kidney deficiency. Their symptoms include scanty pale menstrual blood to as little as a few drops, accompanies with dizziness and vertigo,

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										palpitation, withering complexion, empty dropping sensation of abdomen; scanty thin pale/dark red menstrual blood, low back ache, heel pain, dizziness, tinnitus, cold abdomen, profuse nocturnal urination.
	Delayed periods				x			x	x	This symptom may indicate **interior excess** and **interior deficiency** patterns. **Interior excess** pattern includes patterns of cold in blood, and Qi stagnation. Their symptoms include delayed period with scanty amount and dark colour with clots, cold abdominal pain alleviated by heat, aversion to cold, cold limbs; distending pain in abdomen/chest/hypochondriac regions/breast. **Interior deficiency** pattern includes patterns of deficient cold, and blood deficiency. Their symptoms include delayed period with pale red thin scanty blood, no clots, dull abdominal pain, prefers heat and being pressed, low back ache with weakness, clear profuse urination, loose stool or diarrhoea, dizziness, vertigo, palpitation, somnolence.
	Early periods				x		x	x	x	This symptom may indicate patterns of **interior deficiency** or **interior excess**. The **interior deficiency** pattern includes patterns of Qi deficiency, and deficient heat. Their symptoms include early menstruation with increased pale thin blood volume, fatigue, empty dropping feeling in abdomen, poor

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
										appetite, loose stool, the early menstruation may accompany with scanty/excess amount of red thick blood, malar flush, feverish sensation in the palms/soles. The **interior excess** pattern includes patterns of excessive Yang with heat in the blood, and CM liver Qi stagnation with heat in the blood. Their symptoms include large amount of early menstruation with large amount thick deep red/purple colour blood, chest stuffiness, red face, dry mouth, short yellow urination, dry stool, distending abdominal pain, distending sensation in the breast, irritability, grumpiness, dry mouth, bitter taste in the mouth.
	Irregular periods				x			x	x	This symptom may indicate **interior excess** or **interior deficiency** patterns. **Interior excess** pattern includes CM liver Qi stagnation pattern. The accompanying symptoms include irregular period with either scanty/large amount of purple red blood and clots, the menstrual blood flow is unsmooth, distending pain in chest/breast/hypochondriac region/abdomen, stuffiness in epigastric area, sigh often, hiccup, poor appetite. **Interior deficient** pattern includes CM kidney deficiency pattern. The accompanied symptoms include irregular period with scanty dark thin blood, LBP, dizziness, tinnitus.
	Excessive				x	x			x	

Item category	Items	CM eight guiding principles								
		Yin	Yang	Exterior	Interior	Cold	Heat	Deficient	Excess	Comments
	watery discharge									
	Yellow discharge				x		x		x	Damp heat retention

*Pain character in italicised font indicates no possible CM explanation.
Information extracted from CM diagnosis [38 (p99)], CM internal medicine [134(p108,114,115,121-123,144,145,152-154,171, 172, 205, 206)], CM gynaecology [1026(p23,37-42,44-5,47-51,55-7)], Differential diagnosis of symptom in CM [1025(p330)], and Chinese medicine surgery[1027(p20-21)]

CM: Chinese medicine
LBP: low back pain

Of all of the categories, there are some symptoms that maybe excess/deficiency/heat or cold. To determine the pattern, the other symptoms are taken into consideration. For example, constipation accompanied with swollen, red, and hot joints is due to excessive heat whereas constipation accompanied with pain worse at night and night sweating is due to Yin deficiency. There are some symptoms not explainable from a CM perspective, such as pain worse at lunch time and pain worse in the afternoon. The purpose of these symptoms is to identify if there are new symptoms related to the current CM understanding and not currently understood by CM; and to identify the essential CM information needed to understand CMP.

This first version of CMPQ has the following strengths.

1) Standard textbooks and specialised books on pain in CM were searched to identify items. This ensured CM relevant information was used rather than non-CM relevant information such as in RMDQ.

2) Items were categorised enabling easy comprehension.

3) The questionnaire was designed from the CM perspective instead of the Western medicine perspective as is the McGill pain Questionnaire. This made the CMPQ suitable to assist CM pattern identification.

The following chapters describe the next stages in the development of CMPQ and how these accompanying symptoms and other symptoms were used to derive CM patterns in a statistical manner.

6. Initial development of CMPQ

6.1 Introduction

Chinese medicine views CMP different from Western medicine, in which it uses four diagnostic techniques to collect data on pain and non-pain symptoms and signs of patients then groups those signs and symptoms into different types or pattern [1020(p981-1047,1059-1118)]. The main part of the consultation is enquiry, which refers to obtaining data from patients through an interview. Other methods are palpating, smelling/listening and observing. Chinese medicine questionnaires can be used to collect data relevant to CM diagnosis, however this method is limited to gathering answers from the inquiry part of consultation [1028]. Relying on questionnaires alone has been found to be sufficient to make initial pattern identification [1029].

A standardized CM questionnaire documents the symptoms and signs of a patient, aids the consistency of the questions asked each time and assist in assessment of the changes or treatment outcomes [1028]. It is necessary for the CM questionnaire to achieve responsiveness which refers to the ability to detect significant important changes over time [997]. A CM pain questionnaire should also contain questions on location of pain, quality of pain, pattern of pain occurrence (rhythm), aggravating and alleviating factors of pain, and accompanying non-pain symptoms. From the data gathered, the CM practitioner is able to differentiate the patients' symptom presentation into a CM pattern. Such pattern can then be used to guide setting up treatment principle and the appropriate treatment.

In Chapters four and five, methods of questionnaire development and item generation of CMPQ were described. This chapter aimed to evaluate the properties of CMPQ, including various forms of validity, internal consistency, reproducibility, responsiveness, interpretability, and avoid "floor and ceiling effect". These criteria are listed in Table 6.1. A good questionnaire should achieve most of these aspects in its development.

Table 6.1 Essential properties of a questionnaire

Property	Definition	How to achieve it
Item generation	Generating questionnaire items that are relevant to the questionnaire itself	The items can be generated through 1) focus groups [1000(p18-23)], 2) key informant interviews [1000(p18-23)], 3) clinical observation [1000(p18-23)], 4) theory [1000(p18-23)], 5) research [1000(p18-23)], and 6) expert opinion [1000(p18-23)].
Content validity	The questionnaire items are representative to the concept of interest [997].	Describe the measurement aim of the questionnaire (e.g. discriminative, evaluative, or predictive) [997], the population targeted, the concept the questionnaire is trying to measure [997], and make sure the interpretability of the questionnaire items can be achieved by a 12 year old [997].
Construct validity	"a framework of hypothesis testing based on the knowledge of the underlying construct"[1000(p257-261)]	Comparing the score with another questionnaire that measures the same concept [997].
Criterion validity	How the score of the questionnaire relates to a gold standard [997].	Compared the questionnaire results with another validated questionnaire and see if the results are similar.
Face validity	The questionnaire looks like measuring what it is supposed to measure [1000(p82)].	Give the questionnaire to someone in the field and ask them if they think this questionnaire is assessing what it appears to measure.
Internal consistency	The items measuring the same concept in the questionnaire are correlated [997].	By using statistical software to analyse the data and achieve Cronbach's $\alpha \geq 0.70$.
Agreement (test-retest reliability)	The similarity between a person answering the questionnaire and repeat the questionnaire again in a short time when there is no change in this person's condition [997].	By using statistical software to analyse the data with the correlation coefficient ≥ 0.70.
Inter observer reliability	The degree of agreement between observers [1000(p92)].	By using Cochran's Q test and achieve kappa > 0.41.
Reliability	The ability of the questionnaire to distinguish one patient from another [997].	By using intra-class correlation coefficient and achieve at least 0.70 for continuous data or using weighted Cohen's Kappa coefficient and achieve at least 0.70 for ordinal data [997].
Responsiveness	The ability to detect clinical important changes over time [997].	By using statistical analysis to find out if longitudinally, the questionnaire can detect clinical important changes.
Interpretability	Defining the qualitative meaning of the quantitative score from the questionnaire [1030].	Defining the meaning of the scores, if it is a numerical scale, such as Beck et al. assigned 0-13 as minimal range, 14-19 as mild depression, 20-28 as moderate depression, and 29-63 as severe depression for BDI-II [1006].
Floor and ceiling effect	The number of participants who achieve the best or the worst possible scores [1031].	Looking at the results of the survey, if there are more than 15% of participants who achieved either the best or the worst scores, then there are ceiling/floor effect.

For responsiveness, as the EA protocol (described in Chapter 8.2.1 Participants (p. 260)) aimed at enhancing the release of endorphin, reducing OM use and the side effects of OM, it was necessary to evaluate if the participants responded to EA in terms of reducing the side effects of OM.

The aims of this chapter were to

1) Test the initial version of CMPQ on the CMP patients who used OM for pain control;

2) Evaluate its content validity, face validity, internal consistency, reproducibility(test-retest reliability), and responsiveness;

3) identify common pain and non-pain symptoms of those patients.

6.2 Methods

6.2.1 Participant recruitment

As outlined in Chapter 4.2.1 Participant identification (p. 141) and Chapter 0

Inclusion and exclusion criteria (p. 141), participants were identified from patient case records of Caulfield Hospital, Royal Melbourne Hospital, local GP/specialist referral, and advertisements. Participants who fulfilled the inclusion and had none of the exclusion criteria were recruited into the EAOM trial. Of the participants, 101 completed the CMPQ at both pre-baseline and baseline weeks, and were included for initial CMPQ development.

6.2.2 Item generation and item reduction

The CMPQ items were generated in Chapter five. The questionnaire items were of dichotomous nature as CM diagnosis depends on the presence of a symptom/sign. Items selected by less than 5% of participants were removed [995].

6.2.3 Validity

6.2.3.1 Content validity and face validity

Content validity was evaluated by asking the RCMRG researchers (composition described in

Chapter 4.3.2 Validities (p. 144)) if the measurement aim, target population, concept measured, item selection and reduction, and the interpretability of the items of CMPQ fulfilled the content validity.

Both content and face validities were evaluated by asking the RCMRG researchers if they agreed with 1) CMPQ measured CMP and other symptoms, 2) CMPQ was appropriate for such measurement, 3) would the CMPQ be appropriate for assisting CM pattern identification based on the CM eight guiding principles, and 4) did CMPQ appear to be measuring the symptoms of CMP and other symptoms?

6.2.3.2 Criterion validity

Criterion validity refers to comparison with another gold standard [997]. If the results are similar/same, then such criterion validity is achieved. E.g. developing a new QoL measurement and comparing it with SF36. If testing this newly developed QoL measurement on a person resulting in high QoL and this person also scores high on SF36. Such newly developed QoL questionnaire has achieved criterion validity. As there was no gold standard for CM pain diagnosis. The diagnosis of the CM pattern relied on the CM practitioner to identify. Criterion validity was not tested.

6.2.4 Internal consistency

Internal consistency was assessed by using SPSS version 22 on the pre-baseline week data. Reliability analysis was used to assess the internal consistency of pre-baseline week data. Such analysis would produce Cronbach's α. Cronbach's $\alpha \geq 0.7$ indicated a good internal consistency [997].

6.2.5 Reproducibility (agreement)

Statistical Package for Social Science was used to assess agreement (test-retest reliability). The interval between the test and retest assessments was four weeks between pre-baseline and baseline weeks. During the four weeks, the participants were told not to change any of their medication intake, life style, or receiving new treatment for their pain.

6.2.6 Responsiveness

Chi square test was first carried out to assess if there were significant differences between REA

and PMM alone groups in symptoms related to side effects of OM during baseline week (Table 6.2). The comparison of REA and no-EA groups provides the opportunity to assess which of the side effects of OM, including fatigue, constipation, drowsiness, dizziness, nausea, night sweating, insomnia, nightmare, skin itch, dry mouth, anxiety, blurred vision, vomiting, and profuse sweating, responded to REA treatment. This responsiveness section only assessed REA and PMM alone but not SEA due to it was not intended to assess the placebo effect.

Table 6.2 CMPQ symptoms related to side effect of OM

Domain	Symptom
Pain aggravator	bad night sleep, stress, being emotional, sex
Pain alleviator	bowel movement, sleep
Other symptoms	insomnia, night sweating, irritable, dry stools, constipation, dry skin, feeling tired easily, sigh often, sweat upon mild activities, feeling depressed, reflux, nausea, dizziness, skin itch

Cochran's Q test was then used to test if there were significant changes in these symptoms from baseline, mid treatment, to end of treatment weeks. Only items with a p value <0.1 were considered significant. Such approach had been used for studies with small sample sizes [1032]. Only REA and PMM alone groups' participants who provided data for all the three time points (baseline, mid treatment, and end of treatment weeks) were included for responsiveness assessment. Both groups received OM reduction schedule which aimed to have participants to reduce their OM usage from baseline week onwards and either use the least amount of OM or no OM by the end of treatment week. Electro acupuncture treatment was designed to help reducing pain, increasing endogenous opioid release and reducing side effects of OM (Please see Chapter 2.7.1 Mechanisms of acupuncture (p. 45) for details). Real EA group received its respective treatment twice per week from baseline week to week eight, once per week for week nine and ten (mid treatment week), and once every second week for a further two treatments from week 11 to end of treatment week for a total of 12 treatments. It was expected side effects of OM addressed would respond to the REA treatment. The responsiveness test was assessing if the symptom/item had significant changes but not whether the change was improvement or deterioration.

Comparison with the side effects of OM, as recorded in the pain and medication diary (Appendix 20), was carried out to compare the responsiveness of CMPQ and participant's self reported side effects of OM.

6.2.7 Interpretability

Due to the nature of the CMPQ, there was no score used. The interpretability relied on the practitioners to do CM pattern identification based on the symptoms checked by the participants and the CM eight guiding principles. If practitioners diagnosed CM pattern based on the CM eight guiding principles differently for the same CMPQ, this indicated the subjectivity of CM pattern identification diagnosis. And the interpretability was left to the discretion of the CM practitioner. This initial CMPQ development did not assess the interpretability.

6.2.8 Floor and ceiling effect

Due to there is no score used for this CMPQ. Floor and ceiling effect was not assessed.

6.2.9 Data collection

Participants were asked to complete the demographic questionnaire, CMPQ, BDI, SF36, RMDQ, and pain medication diary. Pain medications were divided into OM and non-OM. Opioid medications were converted into morphine equivalent dose based on the conversion ratio [1033] whereas non-OMs were converted based on Medication Quantification Scale version (MQS) III [1034]. The non-OMs used by each participant were given a summed score derived from the multiplication of the detriment weight and the relative dosage scores [1034]. The score derived from MQS III was used to evaluate the class and dosage of medication usage in order to minimize toxicity, drug-drug interactions and adverse events [1034]. Except for pain medication diary was completed daily, other questionnaires were completed when participants commenced their participation (pre-baseline week, except for SF36, and RMDQ which was not completed in pre-baseline week), four weeks later (baseline week), mid treatment week, and end of treatment week (Table 6.3). These data were collected either at Caulfield Hospital, Royal Melbourne Hospital, Discipline of Chinese medicine, RMIT University, or at the participating CM clinics by the personnel involved in this research project, or by post. Chinese medicine pain questionnaire data were entered and double checked by research personnel. Missing data were reported and removed from analysis. No other methods (e.g. intention to treat, or mean score of all participants) were used for CMPQ missing data. For other questionnaires, last value carried forward was used.

Table 6.3 Trial procedure and outcome assessments

EAOM trial periods*	Procedures			Outcome assessment
Initial screening for eligibility assessment	All potential participants with CMP were assessed for eligibility by MDs			
Baseline period W1-W4	All potential eligible participants			Demographic data, Pain and Medication Diaries W1-W4 Daily and Patient Information Questionnaire, BDI, CMPQ, Pain Medication Questionnaire
	Randomisation of eligible participants			
Treatment period W5-W8 2 EA treatments/week **W9-W10 1 EA treatment/week** **W11-W14 1 EA treatment/2 weeks**	REA	SEA	PMM alone	Pain and Medication Diaries was completed daily from baseline to end of treatment weeks and other measures for baseline, mid treatment and end of treatment weeks, including CMPQ, BDI, SF36, and RMDQ.

Information extracted from [1]
*The EAOM trial periods are different from the CMPQ time points (Figure 1.2, p. 5).
CMP: Chronic musculoskeletal pain
MD: Medical doctor
W: week
BDI: Beck Depression Inventory
CMPQ: Chinese medicine pain questionnaire
SF36: Medical outcome short form health survey 36 items
RMDQ: Roland Morris Disability Questionnaire

6.2.10 Statistical analysis

Data were entered into SPSS version 22 for analysis. Frequency analysis was used to assess the frequency of occurrence of each questionnaire items as well as item reduction (items selected by less than 5% of participants). Reliability analysis, in the scale command, was used for test-retest reliability. Split half model was chosen and in the statistics button, scale was chosen for "descriptive for", correlation was chosen for "summaries", all other options were not checked/selected. Items that might contribute to discrepancies in the total number of items between pre-baseline and baseline weeks were removed from the analysis in both pre-baseline and baseline weeks.

For internal consistency, the reliability analysis was also used. This time "alpha" was chosen for the model and in statistics, "item", "scale", and "scale if item deleted" were checked for "Descriptives for". "Correlation" was checked for "inter item". All the other boxes were

unchecked.

For responsiveness, Chi square test was first used to compare if there was significant difference between REA and PMM alone groups. Crosstabs in “Descriptive statistics” was used. In the statistics option, observed was checked in “counts”, row, column, and total were checked in “percentages”. In format option, ascending was selected for “row order”. Treatment group was put into “row” box and all other symptoms related to side effects of OM were put in “column” box.

Subsequently Cochran’s Q test was used to assess changes amongst baseline, mid treatment, and end of treatment weeks for responsiveness. Syntax was used in SPSS for all the symptoms listed in Table 6.2. Example of the syntax was as following:

```
NPAR TESTS

  /COCHRAN=ITEMA@W5 ITEMA@W10 ITEMA@W14

  /MISSING LISTWISE.
```

Repeated MANOVA was carried out to evaluate the change of side effects of OM severity according to pain and medication diary between baseline and end of treatment weeks. Only participants who provided data for both baseline and end of treatment weeks were included for the analysis.

6.3 Results

6.3.1 Content validity and face validity

The first draft of CMPQ was presented to the RCMRG researchers and they agreed that CMPQ assessed CMP and the accompanying symptoms of CMP and CMPQ was appropriate for such assessment, data from CMPQ could be used to assist CM pattern identification. Based on these, the content validity was achieved.

For face validity, CMPQ had been presented to the RCMRG researchers as of content validity.

The researchers agreed this questionnaire appeared to measure the symptoms and signs of patients who had CMP which was essential in the clinical diagnosis process.

6.3.2 Internal consistency

The results from the analysis showed the Cronbach's α to be 0.919 or 0.935, depending on if pain regions were included. This indicated a high level of internal consistency (Table 6.4). If each section was analysed separately, then pain quality, pain rhythm, and some of the individual pain regions were of a lower level of Cronbach's α (Cronbach's α<0.70) [1035].

Table 6.4 Internal consistency as assessed using Cronbach's α (n=101)

Domains	Cronbach's α	Cronbach's α based on standardized items	Number of items
All domains, except for pain regions	0.919	0.914	127
All domains, including pain regions	0.935	0.931	159
Pain region – head	0.742	0.728	7
Pain region – upper limb	0.763	0.760	6
Pain region – lower limb	0.793	0.800	9
Pain region – front of the body	0.384	0.409	5
Pain region – back of the body	0.603	0.604	5
Pain region – all	0.862	0.855	32
Pain quality	0.327	0.390	12
Pain rhythm	0.344	0.436	11
Pain aggravators	0.817	0.783	25
Pain alleviators	0.725	0.692	34
Accompanied symptoms	0.883	0.884	45

6.3.3 Reproducibility

6.3.3.1 Agreement (test-retest reliability)

For test-retest reliability, there were 27 items not scored by any participants in pre-baseline week and/or baseline week assessments and caused the item numbers uneven in the analysis. These items were listed in Appendix 21 and removed from test-retest reliability analysis.

Test-retest reliability have been shown to have a high reliability for the overall questionnaire (correlation coefficient=0.846) (Table 6.5). When individual domains were compared, they were all showing a high level of reliability (correlation coefficient >0.7) (Table 6.5) except for pain quality and pain rhythm domains where the domains showed correlation coefficient ranged

between 0.49 – 0.556 (Table 6.5). This indicated overall, the entire questionnaire was reliable but the pain quality and pain rhythm domains were not that reliable (e.g. patients did not choose the similar description on the repeated test). When pain regions were assessed altogether (Table 6.5) and when they were individually assessed (Table 6.6) all showed similar results to the entire questionnaire and subgroup assessments where the more items in the domain, the stronger the correlation between the two assessment times and vice versa.

Table 6.5 Test-retest reliability - Overall

Domains			Overall	Pain aggravators	Pain alleviators	Other symptoms	Pain regions	Pain rhythm	Pain quality
Cronbach's Alpha	Pre-baseline week	Value	0.934	0.82	0.725	0.883	0.862	0.328	0.327
		N of Items	155[a]	23[a]	34[a]	44[a]	32[a]	10[a]	12[a]
	Baseline week	Value	0.941	0.815	0.739	0.877	0.878	0.369	0.505
		N of Items	155[b]	23[b]	34[b]	44[b]	32[b]	10[b]	12[b]
	Total N of Items		310	46	68	88	64	20	24
Correlation Between Forms			0.846	0.721	0.73	0.822	0.808	0.49	0.556
Spearman-Brown Coefficient	Equal Length		0.916	0.838	0.844	0.902	0.894	0.657	0.714
	Unequal Length		0.916	0.838	0.844	0.902	0.894	0.657	0.714
Guttman Split-Half Coefficient			0.916	0.838	0.844	0.902	0.893	0.657	0.707

a denotes pre-baseline week items
b denotes baseline week items

Table 6.6 Test-retest reliability - subdivided pain regions

Domains within pain regions			**Head**	**Upper limbs**	**Lower limbs**	**Front of the body**	**Back of the body**
Cronbach's Alpha	**Pre-baseline week**	Value	0.742	0.763	0.793	0.384	0.603
		N of Items	7[a]	6[a]	9[a]	5[a]	5[a]
	Baseline week	Value	0.787	0.817	0.739	0.51	0.606
		N of Items	7[b]	6[b]	9[b]	5[b]	5[b]
	Total N of Items		14	12	18	10	10
Correlation Between Forms			0.735	0.686	0.729	0.621	0.674
Spearman-Brown Coefficient	Equal Length		0.847	0.813	0.843	0.766	0.805
	Unequal Length		0.847	0.813	0.843	0.766	0.805
Guttman Split-Half Coefficient			0.845	0.811	0.841	0.765	0.805

a denotes pre-baseline week items
b denotes baseline week items

6.3.4 Demographic data of participants

One hundred and eight participants consented to participate in the EAOM trial and 101 provided CMPQ data for both pre-baseline and baseline weeks. Not all participants provided the complete demographic data. The majority of the sample is females (56%), middle aged, born in Australia (62.6%), married (46%), and with a tertiary education (University and TAFE education) (45.5%) (Table 6.7). For most of them, their pain was not related to worker's compensation or a third party claim (75.8%). The average years of pain were 12.92 years. The types of pain the participants had are listed in Table 6.9. Forty two out of 56 females were at or above the age of 51 years, the average age for the onset of menopause [1036].

Table 6.7 Demographic data

Demographic variable		Valid N	Mean (SD) or N (%)	Minimum	Maximum
Age		100	55.62 (12.41)	24	83
Gender	Male	100	44 (44%)	Not applicable	
	Female		56 (56%)		
Female age ≤ 51 years		54	14 (25.9%)		
Female age > 51 years			40 (74.1%)		
Country of birth					
Australia		99	62 (62.6%)	Not applicable	
England			8 (8.1%)		
Scotland			4 (4.0%)		
Holland			2 (2.0%)		
Poland			2 (2.0%)		
Greece			2 (2.0%)		
Egypt			2 (2.0%)		
Bosnia			2 (2.0%)		
The remaining other countries			15 (15.2%)		
In relation to pain					
A workers' compensation claim		99	18 (18.2%)	Not applicable	
A third party accident compensation claim			6 (6.1%)		
Not related to works' compensation claim/third party accident compensation/other legal case			75 (75.8%)		
Marital status					
Married		100	46 (46%)	Not applicable	
Single			19 (19%)		
Separated			7 (7%)		
Divorced			18 (18%)		
De facto			5 (5%)		
Widowed			5 (5%)		

Demographic variable	Valid N	Mean (SD) or N (%)	Minimum	Maximum
Education level				
University	99	26 (26.3%)	Not applicable	
TAFE		19 (19.2%)		
Adult education/CAE		2 (2.0%)		
Others		52 (52.5%)		
Duration of pain (years)	93	12.92 (10.7)	0	52

SD: Standard deviation

6.3.5 Medication

For OMs, on average participants consumed 633 mg morphine equivalent dosage per week whereas the non-OMs, on average participants' MQSII score was 10 per week (Table 6.8).

Table 6.8 Baseline pain medication consumption

Type of medication	Valid N	Mean	SD
Average OM usage of baseline (morphine equivalence, mg/week)	96	633.1	1081.1
Average non-OM pain medication of baseline (based on medication quantification scale, score/week)	96	10.4	7.1

6.3.6 Descriptive data

For pre-baseline week data, the frequency of each item is listed from Table 6.9 to Table 6.15. Females related items are listed in Table 6.12, Table 6.13, and Table 6.15 (only females under the age of 51 years were counted for these items). For pain regions (Table 6.9), majority of the participants (>40%) had LBP, neck pain, hip pain, knee pain, shoulder pain, and middle back pain. Less than 5% of participants described pain at vertex. Most of the participants have seven or more pain regions (55.60%).

Table 6.9 Frequency (percentage) of the regions of pain (n=101)

Pain regions	Frequency	Percentage
Head, neck and shoulder regions		
Neck	**45**	**44.60%**
Shoulder	**42**	**41.60%**
Shoulder blades	24	23.80%
Back of the head	21	20.80%
Sides of the head	14	13.90%
Frontal head	13	12.90%
Vertex	*1*	*1.00%*

Pain regions	Frequency	Percentage
Upper limbs		
Upper arm	29	28.70%
Fingers	27	26.70%
Wrist	22	21.80%
Hand	19	18.80%
Elbow	14	13.90%
Forearm	11	11.00%
Lower limbs		
Knee	**49**	**48.50%**
Hip	**48**	**47.50%**
Thigh	**41**	**40.60%**
Ankle	31	30.70%
Calf	29	28.70%
Front of the leg	25	24.80%
Sole	24	23.80%
Toes	23	22.80%
Heel	18	17.80%
Front of the body trunk		
Groin	17	17.00%
Chest	12	11.90%
Side of the body	12	11.90%
Stomach	10	9.90%
Abdomen	8	7.90%
Back of the body trunk		
Lower back	**79**	**78.20%**
Middle back	**42**	**41.60%**
buttocks	36	35.60%
Between shoulder blades	35	34.70%
Sacrum	28	27.70%
Total number of pain regions		
1	10	9.90%
2	8	7.90%
3	3	3.00%
4	11	10.90%
5	8	7.90%
6	7	6.90%
7-10	20	19.90%
11-15	22	21.80%
16-20	11	10.90%
21-29	3	3.00%

Items greater than 40% were bolded and items less than 5% were italicised.

For pain quality (Table 6.10), majority of participants (>40%) described their pain as sharp, in a fixed location. Participants rarely described their pain quality as “not known”.

Table 6.10 Frequency percentage of pain quality (n=101)

Pain quality	Frequency	Percentage
Sharp	**59**	**58.40%**
Fixed location	**43**	**42.60%**
Dull pain with weakness	38	37.60%
Numbness	32	31.70%
Burning	28	27.70%
Dull	24	23.80%
Moving from one spot to another	18	17.80%
Hot	17	16.80%
Pulling	17	16.80%
Pricking	13	12.90%
Cold	11	10.90%
Distending	8	7.90%
Not known	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

For pain rhythm (Table 6.11), majority of participants described their pain was there “all the time”, “worse when first get up”. Rarely participants feel their pain rhythm was recurrent, worse at lunch time, or not known.

Table 6.11 Frequency percentage of pain rhythm (n=101)

Pain rhythm	Frequency	Percentage
All the time	**64**	**63.40%**
Wore when first get up	**43**	**42.60%**
Worse at the end of the day	38	37.60%
Fluctuate	28	27.70%
Worse in the afternoon	26	25.70%
Worse during the day, better at night	16	16.00%
Worse at night, better during the day	13	12.90%
Worse in the morning	11	10.90%
Worse at lunch time	*4*	*4.00%*
Recurrent	*3*	*3.00%*
Not known	*2*	*2.00%*

Items greater than 40% were bolded and items less than 5% were italicised.

For pain aggravator (Table 6.12), majority of participants found cold weather, standing, walking, physical work, sitting, lifting, bending, going up/down stairs, bad night sleep, stress,

and household chores aggravated their pain. And their pain rarely was aggravated by "after eating", "being hungry", or the "not known" factors. The three items relate to menstrual period were assessed in females under 51 years of age as per the National Institute of Health's definition of menopausal age [1036]. And the menstruation was neither a frequent, nor a rare factor that aggravated pain.

Table 6.12 Frequency and percentage of pain aggravator (n=101)

Pain aggravators	Frequency	Percentage
Environmental changes		
Cold weather	**54**	**53.50%**
Weather change	**27**	**26.70%**
Hot weather	19	18.80%
Wet weather	14	13.90%
Windy days	6	5.90%
Exercises of sporting		
Standing	**69**	**68.30%**
Physical work	**64**	**63.40%**
Walking	**64**	**63.40%**
Lifting	**55**	**54.50%**
Sitting	**54**	**53.50%**
Bending	**53**	**52.50%**
Going up/down stairs	**45**	**44.60%**
Driving	35	34.70%
Lying down	25	24.80%
Any movement	22	21.80%
Physiological and psychological changes		
Bad night sleep	**52**	**51.50%**
Stress	**49**	**48.50%**
Being emotional	34	33.70%
Being hungry	*4*	*4.00%*
After eating	*1*	*1.00%*
Others		
Household chores	**47**	**46.50%**
Pressure on the area	28	27.70%
Everything	23	22.80%
Sex	20	19.80%
Not known	*1*	*1.00%*
For female patients (n=14)		
Before period	5	35.7%
During period	4	28.6%
After period	2	14.3%

Items greater than 40% were bolded and items less than 5% were italicised.

For pain alleviator (Table 6.13), majority of participants found hot packs, warm/hot shower,

pain killer, resting, and gentle massage alleviated their pain. Cold weather, wet weather, windy days, standing, driving, eating, being hungry, belching, working, sex, everything, or "not known" rarely alleviated their pain.

Table 6.13 Frequency and percentage of pain alleviator (n=101)

Pain alleviators	Frequency	Percentage
Environmental changes		
Hot packs	**58**	**57.40%**
Warm/hot shower	**50**	**49.50%**
Warm/hot bath	31	30.70%
Hot weather	12	11.9
Cold packs	6	5.90%
Cold weather	*2*	*2.00%*
Wet weather	*1*	*1.00%*
Windy days	*0*	*0%*
Exercises of sporting		
Resting	**49**	**48.50%**
Gentle massage	**41**	**40.60%**
Lying down	34	33.70%
Gentle exercise	24	23.80%
Walking	16	15.80%
Sitting	13	12.90%
Any movement	7	6.70%
Driving	*5*	*5.00%*
Standing	*4*	*4.00%*
Physiological and psychic changes		
Pain killer	**80**	**79.20%**
Sleep	34	33.70%
Keeping my mind off pain	31	30.70%
Watching TV	24	23.80%
Being with other people	23	22.80%
Deep breathing	21	20.80%
Pressure on the pain area	20	19.80%
Reading	17	16.80%
Bowel movement	13	12.90%
Alcohol	7	6.70%
Working	*5*	*5.00%*
Eating	*3*	*3.00%*
Being hungry	*1*	*1.00%*
Belching	*1*	*1.00%*
Others		
Keeping busy	35	34.70%
Nothing	11	10.90%
Household chores	6	5.90%
Sex	*3*	*3.00%*
Everything	*0*	*0%*
Not known	*0*	*0%*
For female patients		

Pain alleviators	Frequency	Percentage
Before period	1	7.10%
During period	1	7.10%
After period	1	7.10%

Items greater than 40% were bolded and items less than 5% were italicised.

For other symptoms (Table 6.14), participants often had “feeling tired easily”, insomnia, limited movements, poor concentration, poor memory, feeling depressed, irritable, constipation, and low libido. Participants rarely had mushy stools or belching.

Table 6.14 Frequency and percentage of non-pain symptoms (n=101)

Item	Frequency	Percentage
Feeling tired easily	**70**	**69.20%**
Insomnia	**60**	**59.40%**
Limited movement	**57**	**56.40%**
Poor concentration	**56**	**55.40%**
Poor memory	**49**	**48.50%**
Feeling depressed	**48**	**47.50%**
Irritable	**46**	**45.50%**
Constipation	**45**	**44.50%**
Low libido	**42**	**41.60%**
Night sweating	39	38.60%
Feeling cold easily	39	38.60%
Sweat upon mild activities	35	34.70%
Swollen joints	33	32.70%
Feeling nervous easily	33	32.70%
Feeling hot easily	30	29.70%
Cold hands and feet	30	29.70%
Thirsty	28	27.70%
Need deep breathing	26	25.70%
Reflux	26	25.70%
Frequent urination at night	25	24.80%
Skin itch	24	23.80%
Short of breath	24	23.80%
Frequent urination	24	23.80%
Dizziness	24	23.80%
Poor appetite	23	22.80%
Dry or sore throat	22	21.80%
Dry skin	22	21.80%
Nausea	21	20.80%
Indigestion	19	18.80%
Heavy sensation in the body	18	17.80%
Sigh often	14	13.90%
Red and hot joints	14	13.90%
Cold lower back or knees	14	13.90%
Flushed face	13	12.90%

Item	Frequency	Percentage
Leak when sneezing or cough	13	12.90%
Distention sensation in the abdomen	11	10.90%
Abdominal distention	10	9.90%
Dry stools	10	9.90%
Cold joints	9	8.90%
Stuffiness in the chest	9	8.90%
Catch cold easily	8	7.90%
Hot palms	8	7.90%
Watery diarrhoea	6	5.90%
Mushy stools	*5*	*5.00%*
Belching	*4*	*4.00%*

Items greater than 40% were bolded and items less than 5% were italicised.

For other symptoms related to gynaecological issues (Table 6.15), only "low back pain during or before period" was frequently experienced by those non-menopausal participants. Excessive watery discharge, yellow discharge, light menstrual blood, and early periods were not experienced by any of the non-menopausal female participants.

Table 6.15 Frequency percentage of other symptoms for female patients (n=14)

Item	Frequency	Percentage
Low back pain during or before periods	**6**	**42.90%**
Abdominal pain during or before periods	5	35.70%
Dark blood	4	28.60%
Excessive bleeding	3	21.40%
Light bleeding	3	21.40%
Irregular periods	2	14.30%
Bleeding with clots	2	14.30%
Delayed periods	2	14.30%
Excessive watery discharge	*0*	*0%*
Yellow discharge	*0*	*0%*
Light blood (pink)	*0*	*0%*
Early periods	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Summing up, the rarely selected items included pain at vertex; pain worse at lunch time, recurrent pain; pain aggravated when hungry and after eating; pain alleviated by cold weather, wet weather, windy weather, driving, standing, working, eating, being hungry, belching, sex, everything; accompanying mushy stools and belching. Participants rarely describe their pain quality/rhythm/aggravator/alleviator as "not known".

6.3.7 Responsiveness

As described in the methods section (Chapter 6.2.6 Data collection (p. 187)), only participants who had completed set of data, that was having completed CMPQ at baseline, mid treatment, and end of treatment weeks, could be included in the responsiveness analysis. In total, 39 were included. The difference between 73 (only REA and PMM alone were counted here) at baseline week to 39 at the end of treatment week was due to drop out (n=12), not able to complete the CMPQ (n=12 for REA and n=10 for PMM alone). Due to there was insufficient number of females in each group, items about the gynaecological symptoms were excluded from the analysis.

Chi square test was carried out to identify group differences at baseline week. Of those symptoms listed in Table 6.2 (p. 188), only other symptom – reflux was showing a significant difference (p=0.025) amongst REA and PMM alone. There were 37.5% in REA (n=23) and only 6.3% in PMM alone (n=16) having reflux symptom. All the other symptoms were not different between REA and PMM alone.

Cochran's Q test was used to analyse these 39 sets of data. Cochran's Q test showed the symptoms responded to the REA and PMM alone interventions but not the direction of changes, e.g. improvement/deterioration. The results were as following:

6.3.7.1 Summary for responsiveness

The results of responsiveness are summarised in Table 6.16. Only REA was showing symptoms responding to REA. There were no symptoms responding to PMM alone intervention.

Table 6.16 Summary of baseline, mid treatment, and end of treatment weeks responsiveness comparison for the two groups

Domain	Items show significant responsiveness
REA	
Pain alleviator	bowel movement
Other symptoms	skin itch
PMM alone	
	No symptoms responded to PMM alone.

6.3.7.2 Responsiveness as determined by CMPQ among those in the REA group (n=23)

Table 6.18 shows the p values for the Cochran's Q test for REA in baseline, mid treatment, and end of treatment weeks. Of these, the significant changes are listed in Table 6.17. Only bowel movement in pain alleviator and skin itch in other symptom responded to REA over time.

Table 6.17 Summary of baseline, mid treatment, and end of treatment weeks responsiveness comparison for REA group (n=23)

Domain	Items show significant responsiveness
Pain alleviator	bowel movement
Other symptoms	skin itch

Table 6.18 P values for Cochran's Q test – REA - baseline, mid treatment, and end of treatment weeks (n=23)

Symptoms	p value
Pain aggravators	
Physiological and psychological changes	
Bad night sleep	0.717
Being emotional	0.819
Stress	0.867
Others	
Sex	0.368
Pain alleviators	
Physiological and psychological changes	
Bowel movement	**0.074**
Sleep	0.779
Others	
Sex	0.368
Other symptoms	
Skin itch	**0.097**
Nausea	0.115
Reflux	0.135
Feeling depressed	0.18
Constipation	0.247
Irritable	0.319
Dry stools	0.368
Night sweating	0.549
Sweat upon mild activities	0.549
Dizziness	0.549
Feeling tired easily	0.607
Feeling nervous easily	0.717
Dry skin	0.779
Insomnia	1

Bond indicate significant responsiveness (p value <0.10)

6.3.7.3 Responsiveness as determined by CMPQ among those in the PMM alone group (n=16)

Table 6.19 shows the p values for the responsiveness changes for PMM alone in baseline, mid treatment, and end of treatment weeks. Of them, there was no significant change in any of the symptoms over time.

Table 6.19 P values for Cochran's Q test – PMM alone – baseline, mid treatment, and end of treatment weeks (n=16)

Symptoms	p value
Pain aggravators	
Physiological and psychic changes	
Bad night sleep	0.276
Stress	0.156
Being emotional	0.247
Others	
Sex	0.223
Pain alleviators	
Physiological and psychic changes	
Bowel movement	0.223
Sleep	0.867
Others	
Sex	0.368
Other symptoms	
Feeling depressed	0.223
Skin itch	0.247
Constipation	0.264
Night sweating	0.368
Dry skin	0.368
Sigh often	0.549
Feeling hot easily	0.607
Irritable	0.607
Sweat upon mild activities	0.607
Reflux	0.607
Nausea	0.607
Dizziness	0.607
Feeling tired easily	0.867
Feeling nervous easily	0.867
Insomnia	0.882
Dry stools	1

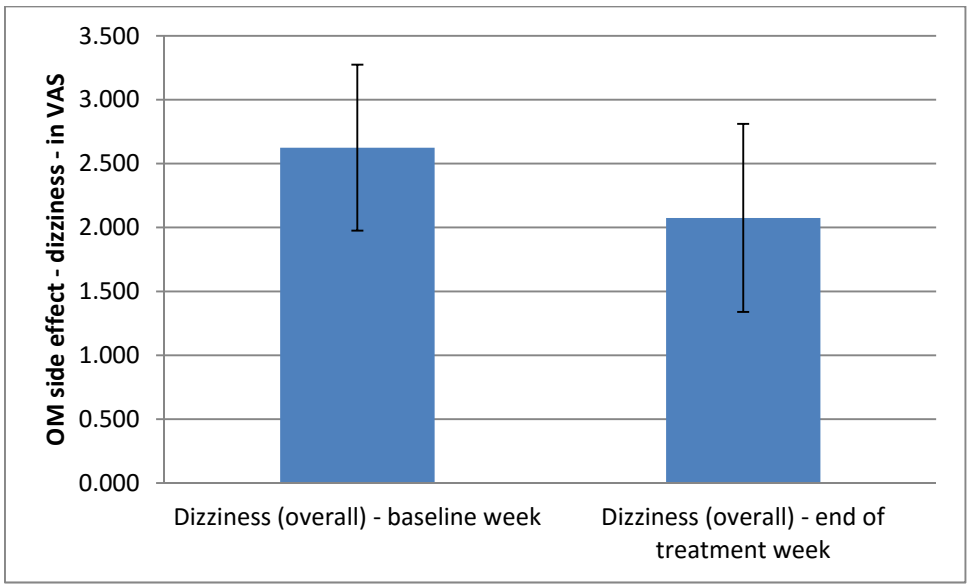
6.3.7.4 Comparison with side effect of OM as recorded in pain and medication diaries

Table 6.20, Figure 6.2 to Figure 6.5 show the repeated MANOVA results and the graphical illustration of changes in side effects of OM severity between baseline week and end of treatment week amongst the REA and PMM alone groups. Apart from dizziness (Figure 6.1), fatigue (Figure 6.2), drowsiness (Figure 6.3), blurred vision (Figure 6.4), and lethargy (Figure 6.5), none of the other OM side effects were showing significant changes over time. And only lethargy reached statistical significant changes over time amongst the two treatment groups where PMM alone reduced more than REA (p=0.080). Not all the participants within the two treatment groups reported experiencing side effects of OM (Table 6.20).

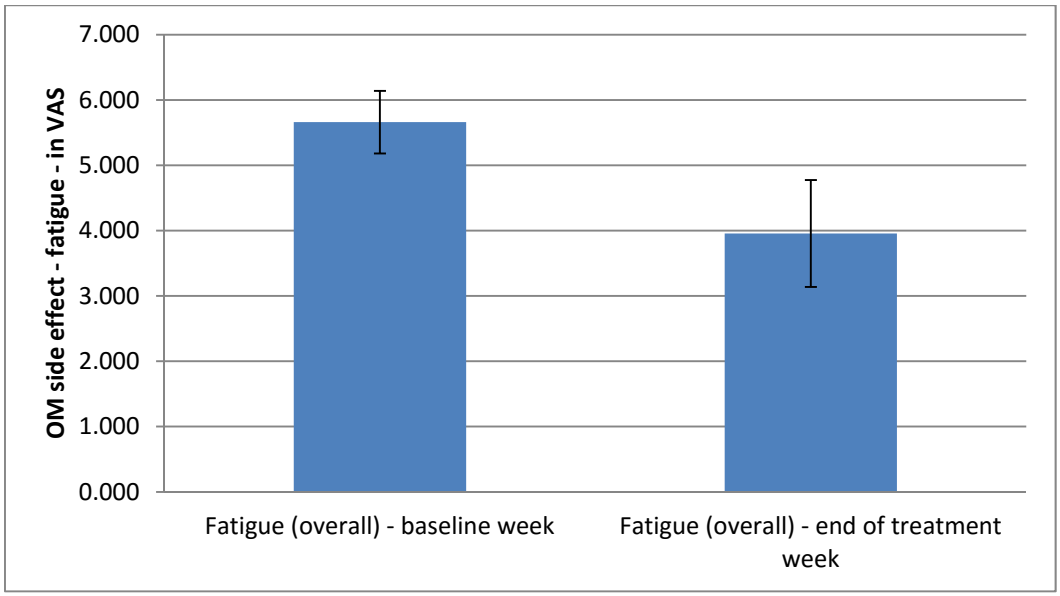
Table 6.20 Repeated MANOVA for side effects of OM amongst the two treatment groups between week 4 and end of treatment week (n=39)

OM side effect	N (total) (n=39)	N (REA) (n=24)	N (PMM alone) (n=16)	Wilk's Λ	F	Hypothesis df	Error df	P value	partial η2
Repeated MANOVA over time									
Nausea	3	2	1	0.949	0.053	1.000	1.000	0.856	0.051
Vomiting	0	0	0	No data					
Dizziness	3	1	2	0.024	40.333	1.000	1.000	**0.099**	0.976
Fatigue	13	6	7	0.659	5.679	1.000	11.000	**0.036**	0.341
Drowsiness	10	4	6	0.465	9.199	1.000	8.000	**0.016**	0.535
Blurred vision	4	2	2	0.169	9.846	1.000	2.000	**0.088**	0.831
Sedation	6	3	3	1.000	0.002	1.000	4.000	0.968	0.000
Lethargy	10	5	5	0.520	7.398	1.000	8.000	**0.026**	0.480
Anxiety	8	3	5	0.702	2.545	1.000	6.000	0.162	0.298
Nightmares	4	2	2	0.569	1.514	1.000	2.000	0.344	0.431
Constipation	9	6	3	0.999	0.007	1.000	7.000	0.937	0.001
Repeated MANOVA over time and the two treatment group									
Nausea	3	2	1	0.500	1.001	1.000	1.000	0.500	0.500
Vomiting	0	0	0	No data					
Dizziness	3	1	2	0.036	27.000	1.000	1.000	0.121	0.964
Fatigue	13	6	7	1.000	0.001	1.000	11.000	0.975	0.000
Drowsiness	10	4	6	0.946	0.459	1.000	8.000	0.517	0.054
Blurred vision	4	2	2	0.591	1.385	1.000	2.000	0.360	0.409
Sedation	6	3	3	0.770	1.196	1.000	4.000	0.336	0.230
Lethargy	10	5	5	0.666	4.006	1.000	8.000	**0.080**	0.334
Anxiety	8	3	5	0.974	0.158	1.000	6.000	0.705	0.026
Nightmares	4	2	2	0.709	0.822	1.000	2.000	0.460	0.291
Constipation	9	6	3	0.950	0.371	1.000	7.000	0.561	0.050

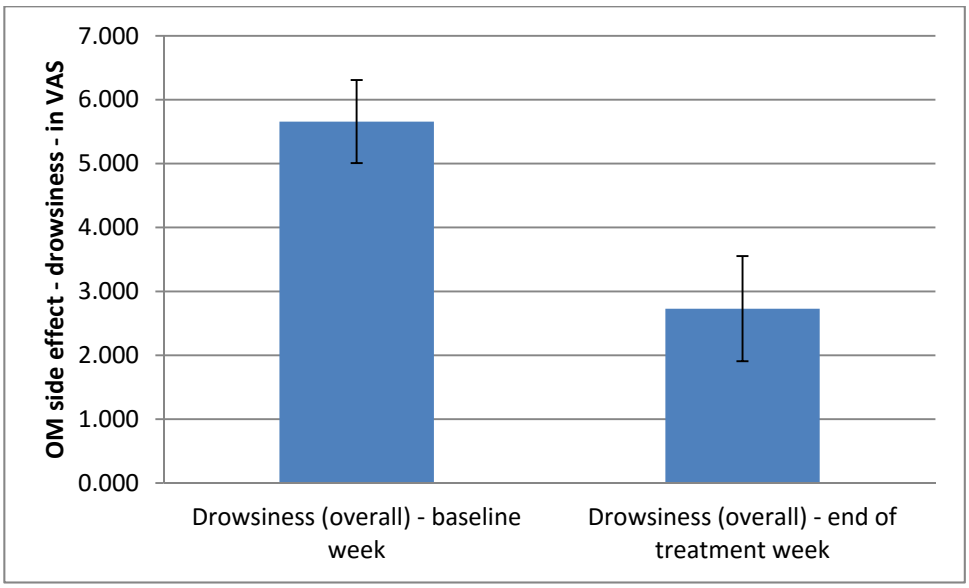
Bold font indicates significant difference (p≦0.1)



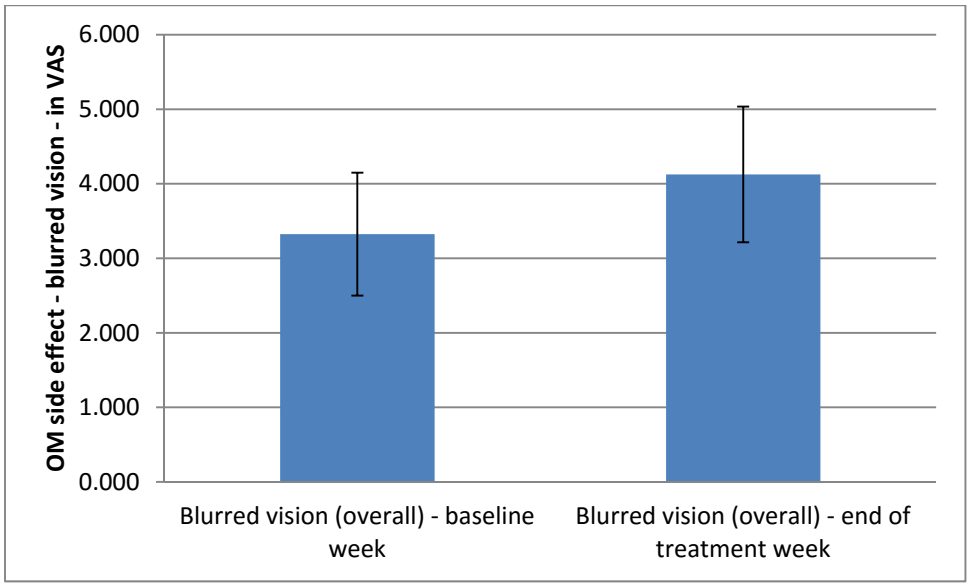
OM: Opioid medication
VAS: Visual analogue scale
Baseline week: Mean: 2.625. Standard error: 0.650
End of treatment week: Mean: 2.075. Standard error: 0.736
Figure 6.1 Changes of side effect of OM - dizziness - between baseline and end of treatment weeks (p=0.099) (n=3)



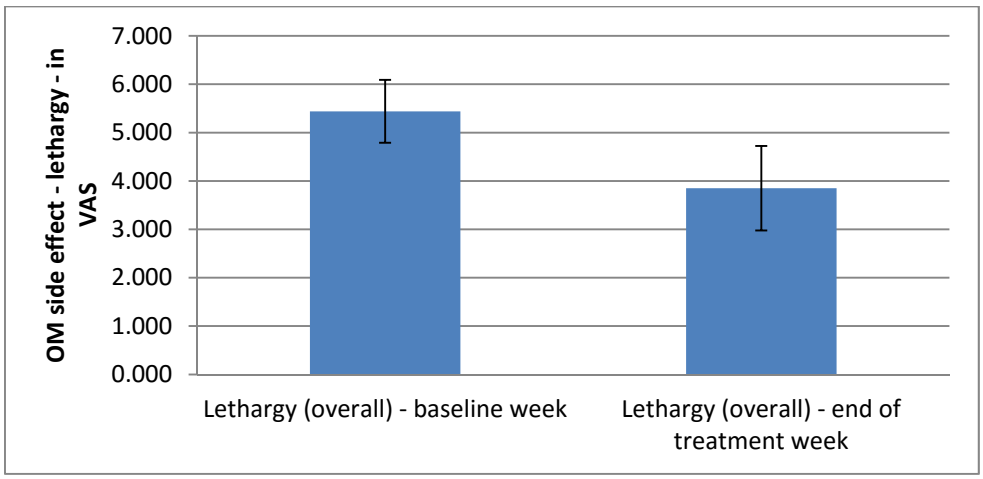
OM: Opioid medication
VAS: Visual analogue scale
Baseline week: Mean: 5.662. Standard error: 0.479
End of treatment week: Mean: 3.956. Standard error: 0.819
Figure 6.2 Changes of side effect of OM - fatigue - between baseline and end of treatment weeks (p=0.036) (n=13)



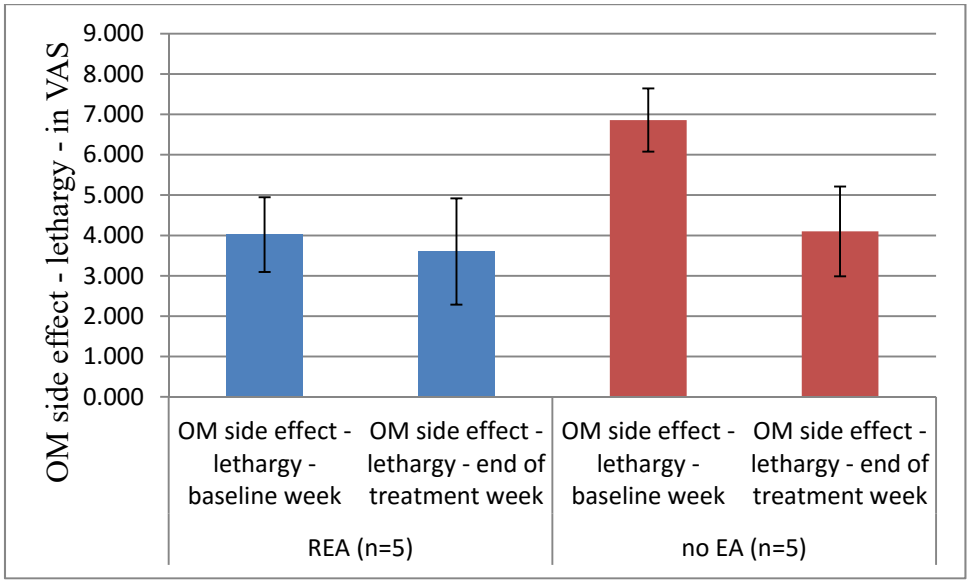
OM: Opioid medication
VAS: Visual analogue scale
Baseline week: Mean: 5.658. Standard error: 0.651
End of treatment week: Mean: 2.729. Standard error: 0.823
Figure 6.3 Changes of side effect of OM – drowsiness - between baseline and end of treatment weeks (p=0.016) (n=10)



OM: Opioid medication
VAS: Visual analogue scale
Baseline week: Mean: 3.325. Standard error: 0.825
End of treatment week: Mean: 4.125. Standard error: 0.910
Figure 6.4 Changes of side effect of OM – blurred vision - between baseline and end of treatment weeks (p=0.088) (n=4)



OM: Opioid medication
VAS: Visual analogue scale
Baseline week: Mean: 5.440. Standard error: 0.650
End of treatment week: Mean: 3.850. Standard error: 0.874
Figure 6.5 Changes of side effect of OM – lethargy - between baseline and end of treatment weeks (p=0.026) (n=10)



OM: Opioid medication
VAS: Visual analogue scale
Blue bars belong to real EA
Red bars belong to PMM alone
REA: Baseline week: Mean: 4.020. Standard error: 0.927. End of treatment week: Mean: 3.600. Standard error: 1.317.
PMM alone: Baseline week: Mean: 6.860. Standard error: 0.927. End of treatment week: Mean: 4.100. Standard error: 1.317.
Figure 6.6 Changes of side effect of OM – lethargy - between baseline and end of treatment weeks amongst the two treatment groups (p=0.080)

6.4 Discussion

6.4.1 Summary of findings

The aim of this chapter was to test the initial version of CMPQ on the CMP patients who used OM for pain control, including 1) evaluating content validity, face validity, internal consistency, reproducibility(test-retest reliability), and responsiveness; 2) collect data on the pain and non-pain symptoms of the patients. The recruited participants were mainly middle aged Australian female who were married and well educated. They consumed OM with morphine equivalence of 633mg/week or 90mg/day on average, which is equivalent to 20 panadeine forte per day. The majority of the participants had an average history of pain 12.92 years and the mean intensity of average pain of 5.5 on a VAS scale. Content and face validities were achieved, internal consistency was high (Cronbach's $\alpha = 0.919$ to 0.935), reproducibility was high (correlation coefficient = 0.846), and bowel movement as pain alleviator and the accompanying skin itch symptom showed responsiveness to REA whereas PMM alone did not have any symptom responding to it. The only side effect of OM, as recorded in the pain and medication diary, showing statistical significant changes over time between REA and PMM alone groups was lethargy. The discrepancy between the side effects of OM recorded in the pain and medication diary and CMPQ (Table 6.17 and Table 6.20) may be due to the pain and medication diary specifically asked patients the side effects of OM whereas CMPQ only asked the presence of symptom. Participant may consider the symptoms they experienced were not side effects of OM.

The recruited participants mainly had sharp pain in their spine, shoulder, lower limb, and mainly at a fixed location. More than 55% of participants had more than seven pain regions. This is similar to widespread pain according to the updated diagnosis of fibromyalgia [979]. To be consistent with the commonly used questionnaire, the future version of CMPQ will incorporate a pain diagram.

The participants had pain all the time or the pain was worse when first got up. Their pains were often aggravated by cold weather, movement (walking, bending, going up/down stair), being static (standing, sitting), physical work (lifting, physical work, household chore), bad night sleep and stress. Their pains were mainly relieved by hot packs/shower, resting, gentle massage, and pain killer. Majority of them experienced multiple non-pain symptoms, including fatigue, insomnia, limited movement, cognitive (concentration and memory) and emotional (depression

and irritability) issues, constipation, and libido issues

6.4.2 Comparing with other CM questionnaires

In this chapter, the CMPQ was developed specifically for CMP patients and tested on CMP patients who use OM for pain relief. A few CM questionnaires have been developed for other health conditions. Park et al. developed a phlegm pattern questionnaire [1037], Zhao et al. developed a sub-optimal health status questionnaire (SHSQ-50) [1038], Lee et al. developed a Yin deficiency questionnaire [1039]. This CMPQ differs from them as more items are included, and it is focusing on CMP patients who use OM for pain relief whereas Park et al. recruited healthy college students who went for a health consultation, Zhao et al. recruited sub-healthy participants who had fatigue for more than three months and healthy participants who did not have fatigue for more than three months. This CMPQ is developed to assist CM clinical consultation for CMP patients whereas Park et al. [1037] and Lee et al. [1039] developed their questionnaires for the CM diagnosis of phlegm pattern and Yin deficiency respectively. And generally questionnaires were specific to one disease/condition, CMPQ aimed to collect broader data from participants to assist CM practitioner with pattern identification about CMP using the CM eight guiding principles.

The CM eight guiding principles (briefly described in Chapter 2.6.2 CM syndrome differentiation (p. 32)) is unique to CM. Briefly the CM eight guiding principles sub groups the patient's symptom presentation into the combination of the eight categories e.g. interior/exterior, cold/heat, deficiency/excess, and Yin/Yang. If a patient presents with lower back pain aggravated by cold weather, alleviated by hot pack, and accompanied with diarrhoea, abdominal distension, and fatigue, such patient has interior cold with deficiency pattern according to the CM eight guiding principles. For the purpose of the CM eight guiding principles, it is necessary to capture sufficiently broader information to cover symptoms for differentiation of different patterns. In this project, the majority participants with SP, lower limb pain, and shoulder pain were included. And according to the search on PubMed on 05/11/2016, there is no other questionnaire developed and utilising the CM eight guiding principles for CM syndrome differentiation.

6.4.3 Comparison with Chapter 3 Systematic review on comorbidity and accompanying symptom associated with CMP conditions

Of the SR chapter, the accompanying symptoms are listed from Table 3.46 to Table 3.48 (p. 126 - 129). The current project included mainly SP, widespread pain, and knee and hip pain which are similar to the three types of pain described from Table 3.46 to Table 3.48. Both the SR and the current project have identified the accompanying fatigue and depression symptoms. In addition, the current CMPQ has identified accompanying symptoms that are frequently occurring but not listed in Table 3.46 to Table 3.48 (p. 126 - 129). The included participants would fall into the three types of CMP based on their pain region presentation. The accompanying symptoms not listed from Table 3.46 to Table 3.48 included poor concentration, poor memory, limited movement, irritable, constipation, and low libido. The possible reason for such information was not found in the SR may be the researchers did not assess them and should include these symptoms for the future research. Although the use of OM may influence the symptom presentation, the CM view on the symptom presentation, as seen in this comparison, would enhance the understanding of the broader picture of the accompanying symptoms of CMP.

6.4.4 The questionnaire properties of CMPQ

The CMPQ results demonstrated good content validity, face validity, a high level of internal consistency (Cronbach's α: 0.912), and test-retest reliability except for domains of individual pain region, pain quality, and pain rhythm due to small item numbers in these domains [1040]. If pain regions were assessed together, then the test-retest reliability was adequate (correlation coefficient = 0.808).

Although two (pain rhythm and pain quality) out of six domains (pain region, pain quality, pain rhythm, pain aggravators, pain alleviators, and other symptoms) did not meet Cronbach's $\alpha \geqslant 0.70$ for internal consistency, the overall CMPQ had a high level of internal consistency. This is considered to be acceptable in questionnaire development as not all domains of a questionnaire needs to have a high level of internal consistency as long as the overall consistency is high [1041]. Apart from that, the Cochran's Q test showed only REA was showing significant change. This indicated symptoms were responding to REA intervention but not PMM alone intervention. On the other hand, it may also mean due to the dichotomous format of the questionnaire CMPQ was not able to detect small changes, e.g. it was not able to detect

small portion of changes, the symptom had to be from presence to absence or vice versa in order to show responsiveness. It is necessary to change the format of question from dichotomous to a likert scale (e.g. 0 – 4) or a VAS like scale (e.g. 0-100) to reflect the degree of variance over time [1042].

The interpretability was not assessed in the development process due to there is no gold standard to compare with for the CM pattern identification. Literature has suggested the medical experiences of the CM practitioners and other factors can influence the CM pattern identification diagnosis [1043]. Expert's CM pattern identification diagnosis is imperfect and can lead to imperfect gold standard bias which gives rise to falsely high sensitivity [1044]. The interpretability of CMPQ requires further research to standardize it.

6.4.5 Item reduction

Within item reduction, there were items rarely selected by participants (Table 6.21). There are symptoms ambiguous to participants, unrelated to pain, contradictory to CM theory, and insufficient participants, or others. The term vertex was rarely selected may be due to the trial recruited CMP patients but not headache patients or maybe this technical term was not understood by participants. The term "not known" in pain quality, pain rhythm, pain aggravator, and pain alleviator was rarely selected. It may be participants all knew what their pain was like or this term was ambiguous to them. Cold weather, wet weather, and windy days all related to a combination type of pathogen in CM understanding – cold, dampness, and wind [1045,1046]. These pathogens cause pain (cold pathogen), make the symptoms to linger (dampness pathogen), or are the guiding pathogen to bring other pathogens to the body or changing frequently such as pain that moves around (wind pathogen) [133(p94-96)]. And due to insufficient participants, gynaecological symptoms were rarely selected by participants. Standing, driving, and working are factors known not to alleviate pain. Belching-related symptoms were rarely selected, and this may be due to the participants did not have belching.

Table 6.21 Possible reasons for rarely selected items

Domain	Symptom	Reasons				
		Not understood or ambiguous	**Maybe pain has nothing to do with appetite**	**Contradictory to CM theory**	**Insufficient female participants**	**Other reasons**
Pain region	Vertex	x				Not target group, this item is suitable for a Headache population
Pain quality	Not known	x				
Pain rhythm	Recurrent					Similar to “all the time”
	Worse at lunch time		x			
	Not known	x				
Pain aggravator	After eating		x			
	Being hungry		x			
	Not known	x				
Pain alleviator	Cold weather			x		
	Wet weather			x		
	Windy days			x		
	Standing					Commonly not an alleviator
	Driving					Commonly not an alleviator
	Eating		x			
	Being hungry		x			
	Belching					Not many participants have belching
	Working					Commonly not an alleviator
	Sex			x		
	Everything	x				
	Not known	x				
Other symptoms	Mushy stools					Side effect of OM is constipation
	Belching					Maybe not related to CMP
Other	Excessive				x	This is perhaps more

Domain	Symptom	Reasons				
		Not understood or ambiguous	Maybe pain has nothing to do with appetite	Contradictory to CM theory	Insufficient female participants	Other reasons
gynaecological symptom	Watery discharge					suitable for pain due to gynaecological conditions,
	Yellow discharge				x	
	Light blood				x	
	Early periods				x	
Total		6	5	4	4	

OM: Opioid medication

6.4.6 Sample size calculation

For sample size, there is no gold rule for a minimum sample size [1047]. Some authors have suggested to have the participant number as five times the total number of items in the questionnaire whereas other authors suggested to have minimum of 100 subjects [1047]. This project followed the minimum of 100 subjects suggestion. Apart for responsiveness where the participants were divided into two groups, the sample size was sufficient for agreement (test-retest reliability) and internal consistency.

The strengths of the project include:

1) a very specific population was targeted, there is no other pain questionnaire developed and recruited participants using OMs as a search in PubMed on 06/11/2016.

2) the total number of participants was over 100.

3) Chinese medicine pain questionnaire contains a broad range of symptoms which is different from other types of outcome measures and it provides clinical data for CM practitioners to differentiate the CM patterns.

4) multiple assessment times allowing for test of responsiveness and test-retest reliability.

The limitations of this project are:

1) there was no other questionnaire or gold standard to compare for construct and criterion validities.

2) most of the females recruited were at the postmenopausal age and items related to gynaecological conditions could not be assessed for reliabilities and validities.

3) the dichotomous format of the questionnaire limited the type of statistical analysis that can be performed.

4) the participants were limited to Victoria region of Australia. The main participants are

Australians. Very few participants from other ethnic background were included in the project.

5) the recruited participants were a small subset of CMP who consumed OM for pain relief.

The limitations of this project affect the validity of the CMPQ to some extend such as most of the females are over the age of menopause. However, researches have shown the prevalence of chronic pain, such as joint pain, widespread pain, and fibromyalgia, increases with age in females and either peaks around or increases further from menopausal age [1048]. The included females are representative of the female population of chronic pain. Furthermore, this limitation should not affect the validity for the non-female related items. The dichotomous format of the data, although limits the assessment of changes, is the basis of how CM doctor diagnoses a patient – whether or not a symptom is present [1019(p873)] rather than giving a score as in most western medical diagnosis.

Implication for future research

The first stage of the CMPQ development demonstrated face validity, content validity, test-retest reliability, and internal consistency. Future development should focus on fulfilling other questionnaire properties that were not assessed in this current project for CMPQ, turning the format into likert scale to reflect the changes after intervention.

The next chapter (Chapter 7 Pre treatment data: pattern identification (all participants) , p. 219) is on CM pattern for the participants where it details the process of sub grouping the symptoms participants presented and the CM patterns, according to the CM eight guiding principles, for the subgroups.

7. Pre treatment data: pattern identification (all participants)

7.1 Introduction

In the last chapter, CMPQ was shown to be reliable, valid, internally consistent, and with some items responded to REA. This chapter will assess if data collected from the CMPQ can be used to help CM pattern identification.

In CM, one disorder or condition may have several clinical patterns or subgroups. For example, the diagnosis of LBP can be subcategorised into five patterns, including LBP due to cold dampness Bi (painful) blockage (寒湿痹阻), LBP due to damp heat retention (湿热阻滞), LBP due to blood stasis (瘀血腰痛), LBP due to Qi stagnation (气滞腰痛), LBP due to CM spleen deficiency (脾虚腰痛), LBP due to CM kidney deficiency (肾虚腰痛) based on a CM textbook [132(p706-708)]. Those patterns are also called CM syndromes. The process of diagnosing a pattern is called CM pattern identification, which heavily relies on data gathered from inspection, auscultation and olfaction, enquiry, and palpation (Table 7.1). For example, if a patient has LBP and accompanied with heaviness of the limbs and the LBP is aggravated by humid or wet weather, such LBP is considered to be the pattern of cold dampness; whereas if the LBP is sharp in nature and the pain is fixed at one location, then such LBP is likely to be a pattern of blood stasis (Table 7.1). Currently the types of patterns of many health conditions outlined in textbooks are established by the experts in the fields. Different textbooks may provide slightly different CM patterns for the same condition [132(p706-708)1022(p1131,1158,1168,1171,1172,1176,1177,1306,1325,1554-1557)1020(p1059-1118) 1021(p308-335)]. For instance, LBP patterns include stagnation of Qi and blood, CM kidney deficiency, CM liver Qi stagnation, invasion of cold and dampness as listed in The Practice of Chinese Medicine [1020(p1059-1118)], and CM kidney deficiency, CM kidney Qi deficiency, CM kidney Yang deficiency, CM kidney Yin deficiency, cold dampness, blood stagnation, CM liver stagnation, CM spleen deficiency as listed in Clinical Handbook of Internal Medicine [1021(p308-335)]. None of the textbooks have applied evidence-based approaches to analyse the clinical data from the patients to develop CM patterns. Does the textbook information reflect the reality is unknown and requires examination.

Table 7.1 Signs and symptoms of different LBP patterns

Low back pain CM patterns	CM eight guiding principles diagnosis	Signs and symptoms
Cold dampness Bi (painful) blockage (寒湿痹阻)	Interior excess cold	Cold LBP with heaviness, difficult to turn around, slowly getting worse, resting does not relieve the pain, pain alleviated by exercise/movement, pain worsened during rainy and cloudy day, greasy white tongue coating, slow and deep pulse
Damp heat retention (湿热阻滞)	Interior excess heat	Low back pain being heavy and hot, pain aggravated by hot days or rainy days, pain alleviated by exercise/movement, dry mouth and thirsty, greasy yellow coating, soft and rapid pulse
Blood stasis (瘀血腰痛)	Interior excess	Sharp LBP at fixed location, worse at night and better during the day, those with mild pain cannot bend easily, those with severe pain cannot turn their body to the side, patient refused to be touched in the tender area, purple dark tongue body, may accompany with ecchymosis in the tongue, unsmooth pulse. Some patients may have a history of trauma.
Qi stagnation (气滞腰痛)	Interior excess	Low back pain comes with pain in hypochondriac region, accompanied with abdominal pain, sigh often, pain aggravated by emotional upset, pain radiates to abdomen, dark tongue body with thin white coating, taut pulse.
CM spleen deficiency (脾虚腰痛)	Interior deficiency	Chronic LBP, heaviness in the body and limbs, lustreless complexion, poor appetite with diarrhoea, white greasy tongue coating, slippery or soft pulse.
CM kidney deficiency (肾虚腰痛)	Interior deficiency	Low back pain manifested as sore and weakness, prefers rubbing, weakness in the lumbar and knee regions, worse after work out, alleviated by bed resting, recurrent in nature. For Yang deficiency, there will be tightness in the lateral abdomen, pale complexion, cold limbs, lassitude and weakness, pale tongue body, and thready deep pulse. For Yin deficiency, there will be vexation and insomnia, dry mouth and throat, malar flush, feverish sensation in the palms and soles, red tongue body with little coating, thready and rapid pulse.

Signs and symptoms extracted from "Chinese medicine internal medicine" [132(p706-708)]
CM: Chinese medicine
LBP: low back pain

For pattern identification, there is an increasing application of scientific methods to sub-group

the diseases/conditions including CM pattern identification in the recent years [1049,1050]. In Western medicine, advanced statistical methods are used. Table 7.2 lists two examples of factor and cluster analyses having been used for sub-group identification for LBP and repetitive strain injury. Cluster analysis is used to sub group LBP into two clusters and repetitive strain injury into eight clusters [1016] based on their clinical presentation and/or other questionnaire outcomes.

Table 7.2 Other pattern identification studies

Study	Participants	Sub grouping methods	Results
Billis et al. [1051]	106 non specific LBP	K-means cluster analysis on a consensus list of potentially discriminatory examination items	2-4 clusters groups were found with 2 clusters being clinical meaningful. One small group (n=24) with more severe clinical presentation whereas the larger group (n=80) were of a less dysfunctional group. The items used for clustering included pain symptom presentation, limitation in range of motion, VAS for pain, RMDQ, Oswestry Disability Index, Fear Avoidance Belief Questionnaire, Hospital Anxiety Depression Scale, and Pain Catastrophizing Scale.
Gold et al. [1016]	700 repetitive strain injury patients	Principal component analysis then K means cluster analysis	Questionnaire contained 118 variables which were grouped into 3 attributes. The 3 attributes included 1) current symptom quality intensity, 2) duration of symptoms in the last week by body region, 3) severity of symptoms in the last week. 8 Clusters were found, 1) mild diffuse musculoskeletal disorder (37.86%) 2) mild bilateral aching stiff neck and shoulder (25.43%), 3) moderate bilateral arm and wrist/hand/finger musculoskeletal disorder (15.56%), 4) severe diffuse musculoskeletal disorder (4.57%), 5) moderate musculoskeletal disorder with highlighted bilateral elbow shooting stabbing pain (11.00%), 6) severe diffuse musculoskeletal disorder with highlighted CNP (2.86%), 7) extreme diffuse musculoskeletal disorder with highlighted pain (1.86%), 8) extreme diffuse musculoskeletal disorder with highlighted CNP (0.86%).

Mild diffuse musculoskeletal disorder: this cluster has mild symptoms without any predominant anatomical area in the upper extremity [1016].
CNP: Coldness, numbness, and paraesthesias
LBP: Low back pain
RMDQ: Roland morris disability questionnaire
VAS: Visual analogue scale

For CM, some authors applied factor analysis and clusters to categorise osteoporosis [1050], hypertension [1052], and non-alcoholic fatty liver disease [1053] (Table 7.3). The authors collected the clinical data from patients instead of simply relying on experts opinions as described in the textbooks[132(in "the guide to use this book")1054]. The resulted sub-groups were meaningful in CM.

Table 7.3 Modern CM pattern identification

Study	Participants	Sub grouping methods	Questionnaire / interview based data collection	Results
Huang et al. [1050]	236 osteoporosis patients	Hierarchical cluster analysis	Questionnaire based	Patients were grouped into four patterns for a better distribution of the data gathered from the four diagnostic methods. The 4 patterns included CM liver and CM kidney Yin deficiency (n=82), CM spleen and CM kidney Yang deficiency (n=71), Qi and blood deficiency (n=46), Qi stagnation and blood stasis (n=37).
Gu et al. [1052]	477 hypertension patients	Two steps cluster analysis	Questionnaire based	Patients were grouped into one of the seven patterns. 1) CM heart and CM kidney Qi deficiency (10.1%); 2) hyperactivity of CM liver Yang (24.1%); 3) deficiency of Yin and Yang (8.4%); 4) stagnation of phlegm dampness (27.1%); 5) phlegm heat (percentage not provided); 6) blood stasis obstructing collaterals (9%); 7) other pattern (not specified) (21.4%);
Fan et al. [1053]	928 non-alcoholic fatty liver disease patients	Factors analysis and cluster analysis	Questionnaire based	The resultant patterns included 1) dampness heat accumulation, 2) CM spleen deficiency with dampness and phlegm, 3) CM liver Qi stagnation and CM spleen deficiency, 4) phlegm stasis accumulation, and 5) CM liver and CM kidney insufficiency

CM: Chinese medicine

In the above mentioned examples, factor analysis and cluster analysis were used. Both are described in Chapter 4.6 Statistical analysis (p.148). Briefly factor analysis is a method used to reduce the items into factors and cluster analysis is a statistical method that is used to group similar items together, named as clusters. When using factor analysis, criteria of KMO, eigen

value, and total factors explained needed to be fulfilled and the factors needed to be interpretable. Currently, sub-categorising CMP patients who use OM for pain control based on CM pattern identification was not found in a PubMed search on 06/11/2016. Such data for CMP patients who use OM for pain control is in need to fill the knowledge gap between the textbook information and the clinical situation.

The aims of this chapter were to

1) establish the CM pattern(s) for CMP patients who use OM for pain control with an evidence-based approach by using the clinical data gathered with CMPQ at the baseline stage of the clinical trial.

2) identifying the differences in demography and pain data among the CM patterns.

7.2 Methods

Inclusion and exclusion criteria

As described in Chapter 4.2.2 Inclusion and exclusion criteria (p. 141), CMP patients who used OM for pain control were included. In addition, only participants who provided baseline week CMPQ data were included.

Outcome measure

Outcome measure included CMPQ completed in baseline week, expression of interest and initial pain questionnaire, which documented patient's pain and demographic data.

Statistical analysis

Baseline week CMPQ data was used. SPSS version 23 was used for statistical analysis. The statistical analysis methods used included frequency analysis, factor analysis, cluster analysis, ANOVA, Chi square, and MANOVA.

Frequency analysis: Frequency analysis was used to evaluate the rarely selected symptoms.

Factor analysis was used to reduce the number of symptoms by principal component analysis.

Factor analysis: Principle component analysis in factor analysis was applied on the items apart from the pain regions. Pain regions were excluded from factor analysis. In CM, apart from low back regions which was associated with the function of CM kidney, pain regions were of no value in CM pattern identification. Varimax rotation was used to rotate the factors. Items that were removed (<5% occurrence in both pre-baseline and baseline weeks) were not used in the factor analysis to prevent distortion to the factors. Factor items with less than 0.5 absolute coefficient values were suppressed. The minimum eigen value depended on the number of factors produced. It was determined the minimum eigen value should explain 60% of the variance [1014(p109)] and at the same time produced adequate factors so the sample size to factor ratio was at least 2:1 [1055]. KMO was used to assess the sampling adequacy [1011(p647)]. The value of KMO ranged from zero to one where zero meant the pattern of correlation in the factors were diffuse and one meant the factors were distinct and reliable [1011(p647)]. The interpretations for KMO were: 0.5-0.7 was mediocre, 0.7-0.8 was good, 0.8-0.9 was great and above 0.9 was superb [1011(p647)]. In factor analysis, the resulted factors may be not interpretable with CM theory. When this occurred, options in factor analysis were manipulated to identify the factors interpretable in CM and fitted into the CM theoretical framework. Factors and factor domains were different. Factors here referred to the individual factors derived from principle component analysis whereas factor domains referred to the characteristics of pain described in Chapter 5.1 Introduction (p. 152).

Cluster analysis: The resulted factors were saved and used in K-means cluster analysis. K-means cluster analysis could only take up scale data but not ordinal data. Scale data referred to data such as VAS for pain where patients can rate from 0 to 10 even to decimals. Ordinal data referred to data rated with a hierarchy in the data. That is to say three is always better/worse than two depending on the question. But there is nothing in between the numbers e.g. no decimals. The resulted factors from factor analysis were scale data - suitable for K means cluster analysis. This referred to the dichotomous data in the CMPQ had been turned into a scale data where there is decimal numbers by factor analysis. This is illustrated in Figure 7.1 and Figure 7.2 where Figure 7.1 shows the original dichotomous data where only zero and one are used and Figure 7.2 shows the resulted scale data showing decimals after factor analysis. Further information about how factors were generated is provided in Chapter 4.6 Statistical analysis (p. 148). Again, different options in K-means clusters were manipulated to identify the interpretable clusters. In the method of K means cluster analysis in SPSS, “classify only” was

selected instead of “iterate and classify” in the end to derive interpretable clusters (Figure 7.3).

	patientname	patientnum...	PQC@W5	PQP@W5	PQD@W5	PQFL@W5	PQMOS@...	PQSH@W5	PQPR@W5	PQNU@W5	PQDU@W5	PQDPW@W5	PQHO@W5	PQBG@W5
36	HarT1015	1015	.00	.00	.00	1.00	.00	1.00	.00	1.00	.00	.00	.00	.00
37	MckJ1016	1016	.00	1.00	1.00	.00	.00	1.00	.00	.00	.00	.00	.00	.00
38	ThuL1017	1017	.	.	.	.	.	.	.	.	.	.	.	.
39	CurA1019	1019	.00	.00	.00	1.00	.00	.00	.00	.00	1.00	.00	.00	.00
40	MicJ1025	1025	.00	.00	.00	.00	.00	1.00	.00	.00	.00	.00	.00	1.00
41	BonK1026	1026	.00	.00	.00	1.00	.00	1.00	1.00	1.00	.00	.00	.00	1.00
42	ZayM1027	1027	1.00	.00	.00	.00	1.00	1.00	1.00	1.00	.00	.00	1.00	.00
43	PeaA1028	1028	.00	1.00	.00	1.00	1.00	1.00	1.00	.00	.00	.00	.00	.00
44	DadJ1030	1030	.00	1.00	.00	.00	.00	1.00	.00	1.00	.00	.00	1.00	1.00
45	GarM1035	1035	.00	.00	.00	1.00	.00	1.00	.00	.00	.00	.00	.00	.00
46	AdaK1037	1037	.00	.00	.00	1.00	1.00	1.00	.00	1.00	1.00	1.00	1.00	.00
47	MulD2002	2002	.00	.00	.00	.00	.00	1.00	.00	.00	.00	.00	.00	1.00
48	QuoE2006	2006	.00	.00	.00	.00	.00	1.00	.00	.00	.00	.00	1.00	1.00
49	BasA2007	2007	.00	.00	.00	.00	.00	.00	.00	.00	.00	1.00	1.00	1.00
50	MarV2009	2009	.00	.00	.00	1.00	.00	1.00	.00	.00	.00	.00	.00	.00
51	PorB2014	2014	.00	.00	.00	1.00	.00	.00	.00	.00	.00	.00	1.00	.00
52	RanB2015	2015	.00	1.00	.00	1.00	.00	1.00	.00	.00	.00	.00	1.00	.00
53	NicF2018	2018	.00	.00	.00	1.00	1.00	1.00	.00	1.00	1.00	1.00	1.00	1.00
54	ConP2021	2021	.00	.00	.00	1.00	1.00	1.00	1.00	.00	1.00	.00	.00	.00
55	GarS2022	2022	1.00	.00	.00	1.00	.00	.00	.00	.00	1.00	.00	.00	.00
56	ShaK2025	2025	.00	.00	.00	1.00	.00	.00	.00	.00	.00	.00	.00	.00
57	HulM2029	2029	.00	.00	.00	.00	.00	1.00	.00	1.00	1.00	1.00	.00	.00
58	EltB2034	2034	1.00	.00	.00	.00	.00	.00	.00	1.00	.00	.00	1.00	1.00
59	OkeD3012	3012	.00	.00	.00	1.00	.00	1.00	.00	.00	.00	.00	.00	.00
60	HutA3013	3013	.00	.00	.00	1.00	.00	1.00	.00	.00	.00	.00	1.00	.00
61	TurC3016	3016	.00	1.00	.00	1.00	.00	.00	1.00	.00	1.00	.00	.00	1.00
62	ConD3018	3018	.00	.00	.00	1.00	.00	1.00	.00	.00	1.00	.00	.00	.00
63	DeaS3020	3020	.	.	.	.	.	.	.	.	.	.	.	.
64	LouM3025	3025	.00	1.00	1.00	.00	1.00	1.00	.00	1.00	.00	1.00	1.00	1.00
65	HarM3027	3027	.00	.00	.00	1.00	.00	.00	.00	.00	.00	.00	.00	.00

Figure 7.1 Original dichotomous data for factor analysis

	patientname	patientnum...	FAC1_1	FAC2_1	FAC3_1	FAC4_1	FAC5_1	FAC6_1	FAC7_1	FAC8_1	FAC9_1	FAC10_1
36	HarT1015	1015	-.37116	-1.08765	-.04322	1.40158	-.92694	-.56379	-.52935	.40379	.23542	-.11999
37	MckJ1016	1016	-1.10618	.58170	-.54097	.66099	.32009	-.84058	-.58180	.69919	.06318	.13695
38	ThuL1017	1017	1.33796	-.19390	1.60415	.96822	1.52688	2.26749	2.85400	.48713	1.93078	-.74379
39	CurA1019	1019	-.58011	-.64560	-.43177	-.66716	-.61137	-.32708	.06051	.15747	-.27238	-.26095
40	MicJ1025	1025	.	.	.	.	.	.	.	.	.	.
41	BonK1026	1026	-.42067	-.96018	-.41942	-.66575	.29782	-.29028	-.06078	-1.24120	-.16857	-.14370
42	ZayM1027	1027	-.49929	.36400	1.25401	-.19689	1.86542	-.23465	1.16706	-.20588	-2.46422	-.75303
43	PeaA1028	1028	-.33950	1.10173	-.46836	-.33062	.04204	2.85832	.42554	-2.46205	1.55414	-1.00548
44	DadJ1030	1030	.39136	-1.42751	.20622	1.13536	-1.26023	.07484	-.55106	1.37324	-.00723	-.78470
45	GarM1035	1035	-1.52127	.32902	-.78924	1.24063	.64312	.57507	1.14338	.55526	-1.20357	-1.28997
46	AdaK1037	1037	-1.00378	-.00606	-.59550	-.09788	.44171	3.37454	.58178	.18037	-.00277	5.04739
47	MulD2002	2002	-.78023	1.19573	-.93773	1.30094	-.77117	.95924	-1.24308	.25921	.49996	.59517
48	QuoE2006	2006	-.57645	-1.19212	-.42485	-1.15088	.56212	1.52039	.42290	-1.17598	-.28548	-.35451
49	BasA2007	2007	.	.	.	.	.	.	.	.	.	.
50	MarV2009	2009	-.58011	-.64560	-.43177	-.66716	-.61137	-.32708	.06051	.15747	-.27238	-.26095
51	PorB2014	2014	-.21948	-.82200	-.10698	-.50093	-.78799	-.40908	.15795	-.12691	-.86323	-.01949
52	RanB2015	2015	.	.	.	.	.	.	.	.	.	.
53	NicF2018	2018	.81773	.94927	2.46973	1.18856	-.49623	.09358	2.63722	.57285	-.48872	.16804
54	ConP2021	2021	.56597	-.17685	-.70923	-.14637	-1.33393	.01388	.16926	-.17144	-.68845	-.30974
55	GarS2022	2022	-.51371	.26319	1.73614	-.00436	.65791	-.75504	-1.75316	.10276	2.21133	.87850
56	ShaK2025	2025	-.91196	-.92878	-.74096	2.00396	.22862	-.40123	-.03709	.25674	-.11008	-.08169
57	HulM2029	2029	.16493	-.42624	-1.42763	1.19393	-.05515	-.43430	-.05912	.12744	.14265	-.60122
58	EltB2034	2034	-.44860	1.83769	.78222	-1.02923	1.30826	.23678	-.72887	.41171	.04978	-.23863
59	OkeD3012	3012	.01903	-.03564	-.53973	-1.28945	-.51027	-.51682	.20885	.56391	-.52879	-.22205
60	HutA3013	3013	.11628	-.90113	-.66486	-.47205	.29709	-.23911	-.21644	-1.75962	-.09694	-.12831
61	TurC3016	3016	-.50161	.37203	-.50349	-.33853	1.35408	.61709	-1.03831	-.45936	.92764	-.01980
62	ConD3018	3018	.	.	.	.	.	.	.	.	.	.
63	DeaS3020	3020	.	.	.	.	.	.	.	.	.	.
64	LouM3025	3025	.76146	.60163	-.36189	-1.13572	-.95773	.51558	-.61502	2.17037	-.60164	.18642
65	HarM3027	3027	-.63561	-.30862	-.46353	-.87476	-.58636	-.18909	.47065	-.70759	-.38282	-.35971

Figure 7.2 Factor analysis turned dichotomous data into scale data with decimals

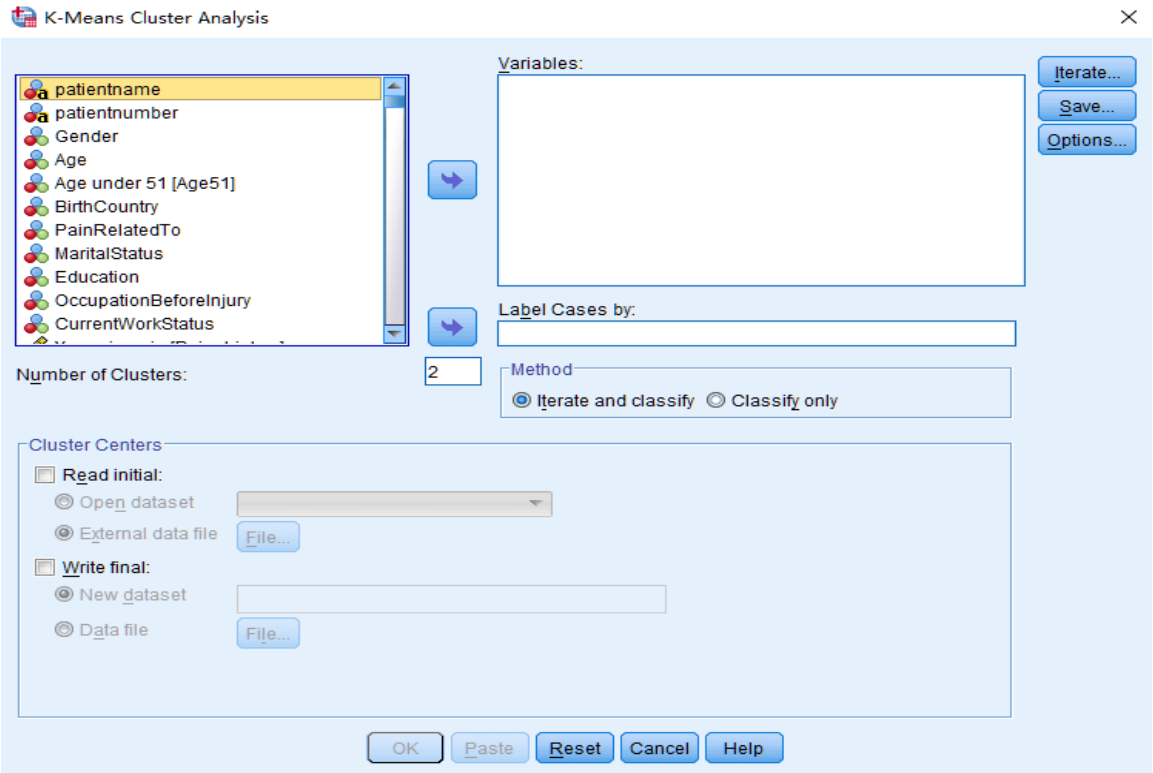


Figure 7.3 The method of K means cluster analysis

To determine the number of clusters, the elbow method described by Gelasakis et al. was used [1056]. The elbow method used Wards method within hierarchical cluster analysis. Within the agglomeration schedule, one needed to find the two stages where the biggest change in distance coefficient occurred. The stage before the biggest change in distance coefficient was subtracted from the sample size. This gave the ideal number of clusters for the K-means cluster analysis. For example, the biggest change occurred in step 12 as shown in Figure 7.4. Then number of cluster was 16-12 = 4.

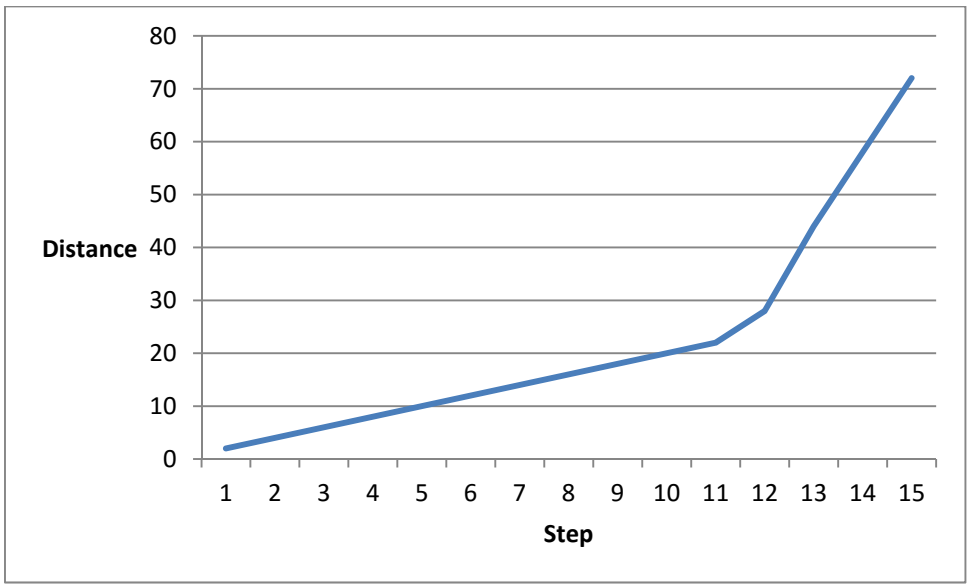


Figure 7.4 Example of the elbow method

Chi square, ANOVA, and MANOVA were used to find out if the identified clusters were of any differences in age, gender, pain history and other data. Specifically ANOVA was used on age, Chi square was used on demographic data and MANOVA was used on pain history, and baseline week data of total pain regions, current work status, average of OM consumption, average of NonOM analgesics, average of average pain intensity, unpleasantness of average pain, RMDQ, total score of BDI, physical health total of SF36, mental health total of SF36, and total SF36 score.

Chinese medicine cluster analysis group researchers of the Discipline of Chinese Medicine within RMIT University reviewed the clusters and related data and provided the CM pattern for them.

7.3 Result

7.3.1 Baseline week frequency analysis

For baseline week, data were available for 106 participants. Frequency of each item was presented from Appendix 22 to Appendix 27. For pain region, the frequently (≥ 40%) occurred pain regions were lower back (77.4%), neck (45.3%), hip (43.4%), knee (40.6%). There was no pain region selected by less than 5% of participants.

Participants often felt the qualities of their pains were sharp (58.5%) and in a fixed location (47.2%) (Appendix 23) and described they had pain all the time (74.5%), and worse when

first got up (40.6%).

Standing (65.1%), physical work (64.2%), walking (62.3%), stress (55.7%), cold weather (54.7%), lifting (53.8%), bad night sleep (52.8%), sitting (51.9%), bending (50.0%), going up/down stairs (50.9%), household chores (50.0%) often aggravated participants' pain. For females (n=15 for females aged under 51), before and during period often aggravated their pain (40% each) whereas after period (6.7%) generally did not aggravate participant's pain (Appendix 24).

Pain killer (80.2%), hot packs (53.8%), resting (44.3%), warm/hot shower (42.5%) often alleviated participants' pain (Appendix 25).

For females (n=15 for females aged under 51), only 26.7% of participants described after period alleviated their pain whereas before and during period did not alleviate their pain (Appendix 25).

For other symptoms, participants' often had feeling tired easily (66.0%), insomnia (53.8%), limited movement (51.9%), poor concentration (50%), poor memory (50%), feeling depressed (45.3%), low libido (43.4%) and constipation (41.5%) (Appendix 26).

For females' other symptoms, none of them were frequently experienced by female participants and no participants had light menstrual blood (pink) (0%), early periods (0%), excessive watery discharge (0%), and yellow discharge (0%) (Appendix 27).

7.3.2 Factor analysis

Items that had a low frequency of less or equal to five percent were removed prior to conducting factor analysis (Table 7.4). All the female related items were removed as only 15 female participants were under the age of menopause.

Table 7.4 Removed items prior to factor analysis

Domain	Items
Pain quality	Not known
Pain rhythm	Recurrent, worse at lunch time, not known
Pain aggravator	Environmental changes - windy days Physiological and psychic changes - after eating Others - not known For female patient - before period, during period, after period
Pain alleviator	Environmental changes - cold weather, wet weather, windy days, Exercises of sporting - standing, driving, Physiological and psychic changes - eating, being hungry, belching, working Others - sex, everything, not known For female patient - before period, during period, after period
Other symptoms	Belching, watery diarrhoea For female patients - abdominal pain during or before period periods, low back pain during or before periods, dark blood, light blood (pink), bleeding with clots, excessive bleeding, light bleeding, delayed periods, early periods, irregular periods, excessive watery discharge, yellow discharge

The KMO values are listed in Table 7.5. All factor domains were of acceptable KMO values (KMO>0.5). The aggravating factor domain was well sampled (KMO>0.7). The total variance explained were all acceptable except for pain rhythm which was close to acceptable.

Table 7.5 Eigen values, total variance explained and KMO

Factor domains	Eigen values	Total variance explained	KMO
Pain quality	1.061	59.84%	0.628
Pain rhythm	1.27	56.76%	0.538
Aggravating factors	1.108	60.77%	0.725
Alleviating factors	1.134	61.80%	0.553
Other symptoms	1.163	62.40%	0.633

KMO: Kaiser–Meyer–Olkin measure

Table 7.6 to Table 7.10 show the results of the factor analysis. There were five pain quality factors (Table 7.6), three pain rhythm factors (Table 7.7), seven pain aggravating factors (Table 7.8), nine pain alleviating factors (Table 7.9), and 12 other symptoms factors (Table 7.10). In total there were 36 factors, resulting in the ratio of the number of participants to the number of factors ratio to almost 3:1. Interpretation of those factors is provided in Table 7.11.

Table 7.6 Pain quality factor analysis (factor unrotated)

Component Matrix[a]					
	Component				
	1	2	3	4	5
Pain quality-cold-wk5					
Pain quality-pulling-wk5					
Pain quality-distending-wk5					
Pain quality-fixed location-wk5		.619			
Pain quality-moving from one spot to another-wk5					.540
Pain quality-sharp-wk5			.534		.510
Pain quality-pricking-wk5				-.547	
Pain quality-numbness-wk5	.724				
Pain quality-dull-wk5		.594		.514	
Pain quality-dull pain with weakness-wk5			-.587		
Pain quality-hot-wk5	.507				
Pain quality-burning-wk5	.684				
Extraction Method: Principal Component Analysis.					
a. 5 components extracted.					

Empty cells means < 0.5 and are suppressed

Table 7.7 Pain rhythm factor analysis

Rotated Component Matrix[a]			
	Component		
	1	2	3
pain rhythm-all the time-wk5	-.772		
pain rhythm-fluctuate-wk5	.826		
pain rhythm-worse during the day, better at night-wk5		.719	
pain rhythm-worse at night, better during the day-wk5		-.540	.528
pain rhythm-worse when first get up-wk5			.510
pain rhythm-worse at the end of the day-wk5			.794
pain rhythm-worse in the morning-wk5		.676	
pain rhythm-worse in the afternoon-wk5			.510
Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.a			
a. Rotation converged in 5 iterations.			

Empty cells means < 0.5 and are suppressed

Table 7.8 Pain aggravator factor analysis

Rotated Component Matrix[a]							
	Component						
	1	2	3	4	5	6	7
Pain aggravator-environmental changes-wet weather-wk5			.833				
Pain aggravator-environmental changes-weather change-wk5			.717				
Pain aggravator-environmental changes-hot weather-wk5					.851		
Pain aggravator-exercises of sporting-standing-wk5							
Pain aggravator-exercises of sporting-walking-wk5	.631						
Pain aggravator-exercises of sporting-lying down-wk5				.618			
Pain aggravator-exercises of sporting-physical work-wk5	.658						
Pain aggravator-exercises of sporting-sitting-wk5				.785			
Pain aggravator-exercises of sporting-lifting-wk5	.675						
Pain aggravator-exercises of sporting-bending-wk5	.741						
Pain aggravator-exercises of sporting-any movement-wk5						.682	
Pain aggravator-exercises of sporting-going up/down stairs-wk5	.627						
Pain aggravator-exercises of sporting-driving-wk5				.625			
Pain aggravator-Physiological and psychic changes-after eating-wk5							-.722
Pain aggravator-Physiological and psychic changes-being hungry-wk5							
Pain aggravator-Physiological and psychic changes-bad night sleep-wk5							
Pain aggravator-Physiological and psychic changes-stress-wk5		.778					
Pain aggravator-Physiological and psychic changes-being emotional-wk5		.766					
Pain aggravator-others-pressure on the area-wk5					.753		
Pain aggravator-others-sex-wk5							
Pain aggravator-others-everything-wk5						.663	
Pain aggravator-others-household chores-wk5	.655						
Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.[a]							
a. Rotation converged in 8 iterations.							

Empty cells means < 0.5 and are suppressed

Table 7.9 Pain alleviator factor analysis

Rotated Component Matrix[a]									
	Component								
	1	2	3	4	5	6	7	8	9
pain alleviator-environmental changes-hot packs-wk5									
pain alleviator-environmental changes-cold packs-wk5		.580							
pain alleviator-environmental changes-hot weather-wk5			.672						
pain alleviator-environmental changes-warm/hot bath-wk5			.595						
pain alleviator-environmental changes-warm/hot shower-wk5									
pain alleviator-exercises of sporting-walking-wk5						.815			
pain alleviator-exercises of sporting-lying down-wk5				.788					
pain alleviator-exercises of sporting-sitting-wk5					.634				
pain alleviator-exercises of sporting-gentle massage-wk5									
pain alleviator-exercises of sporting-gentle exercise-wk5						.566			
pain alleviator-exercises of sporting-any movement-wk5								-.518	
pain alleviator-exercises of sporting-resting-wk5									
pain alleviator-Physiological and psychic changes-deep breathing-wk5		.751							
pain alleviator-Physiological and psychic changes-bowel movement-wk5									.890
pain alleviator-Physiological and psychic changes-pain killer-wk5								.700	
pain alleviator-Physiological and psychic changes-pressure on the pain area-wk5					.689				
pain alleviator-Physiological and psychic changes-keeping my mind off pain-wk5									
pain alleviator-Physiological and psychic changes-being with other people-wk5									
pain alleviator-Physiological and psychic changes-alcohol-wk5							.561		
pain alleviator-Physiological and psychic changes-reading-wk5	.590								
pain alleviator-Physiological and psychic changes-sleep-wk5				.712					
pain alleviator-Physiological and psychic changes-watching TV-wk5	.778								
pain alleviator-others-keeping busy-wk5		.541							
pain alleviator-others-household chores-wk5									
pain alleviator-others-nothing-wk5							-.701		

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.[a]
a. Rotation converged in 23 iterations.
Empty cells means < 0.5 and are suppressed

Table 7.10 Other symptoms factor analysis

Rotated Component Matrix[a]												
	Component											
	1	2	3	4	5	6	7	8	9	10	11	12
other symptoms-swollen joints-wk5												
other symptoms-red and hot joints-wk5								.549				
other symptoms-cold joints-wk5				.653								
other symptoms-limited movement-wk5												.722
other symptoms-distention sensation in the abdomen-wk5		.764										
other symptoms-indigestion-wk5										.646		
other symptoms-heavy sensation in the body-wk5		.576										
other symptoms-cold hands and feet-wk5			.518									
other symptoms-cold lower back or knees-wk5				.789								
other symptoms-feeling cold easily-wk5							.559					
other symptoms-feeling hot easily-wk5												
other symptoms-insomnia-wk5					.553							
other symptoms-night sweating-wk5									.715			
other symptoms-irritable-wk5	.689											
other symptoms-dry or sore throat-wk5												
other symptoms-flushed face-wk5								.681				
other symptoms-hot palms-wk5								.642				
other symptoms-thirsty-wk5			.605									
other symptoms-mushy stools-wk5		.664										
other symptoms-dry stools-wk5												
other symptoms-constipation-wk5	.558											
other symptoms-dry skin-wk5			.624									
other symptoms-leak when sneezing of cough-wk5												
other symptoms-frequent urination at night-wk5					.701							
other symptoms-frequent urination-wk5												
other symptoms-poor concentration-wk5	.660											
other symptoms-poor memory-wk5	.746											
other symptoms-low libido-wk5	.560											
other symptoms-poor appetite-wk5							.756					

other symptoms-feeling tired easily-wk5									.605			
other symptoms-sigh often-wk5												
other symptoms-need deep breath-wk5												
other symptoms-short of breath-wk5						.744						
other symptoms-sweat upon mild activities-wk5												
other symptoms-catch cold easily-wk5											.773	
other symptoms-abdominal distention-wk5		.834										
other symptoms-stuffiness in the chest-wk5						.545						
other symptoms-feeling nervous easily-wk5												
other symptoms-feeling depressed-wk5												
other symptoms-reflux-wk5										.810		
other symptoms-nausea-wk5												
other symptoms-dizziness-wk5			.553									
other symptoms-skin itch-wk5												.512

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.[a]
a. Rotation converged in 27 iterations.
Empty cells means < 0.5 and are suppressed

For the factors extracted above, they were discussed and named based on CM theories about pain by the CM cluster analysis group researchers. Those factors became units enabling cluster analysis and interpretation of the clusters (Table 7.11). Some of the factors were too complicated or too simple there was no name/interpretation given for them.

Table 7.11 Factor names

Domain	Factors	Factor names	Explanation
Pain quality	Numbness, hot, burning	Hot and numb pain	Heat
	Fixed location, dull	Dull pain at fixed location	Possibly Deficiency
	Sharp, dull pain with weakness (-)*	Sharp pain not dull with weakness	Excess, possible blood stasis
	Pricking (-)*, dull	Dull pain	Qi deficiency
	Moving from one spot to another, sharp	Sharp moving pain	Excess, possible Qi and Blood stagnation
Pain rhythm	All the time (-)*, fluctuate	Pain fluctuates	Deficiency
	"Worse during the day, better at night", "worse at night, better during the day"(-)*, worse in the morning	Pain worse from morning to day time and better at night.	Yang deficiency
	"Worse at night, better during the day", worse when first get up, worse at the end of the day, worse in the afternoon	Pain better during the day and worse at all other times.	Yin deficiency
Pain aggravating factor	Walking, physical work, lifting, bending, going up/down stairs, household chores	Worse by exertion	Deficiency, possibly Qi deficiency
	Stress, being emotional	Worse by mental strain	Qi stagnation
	Wet weather, weather change	Worse by wet weather and weather change	Excess, possible dampness
	Lying down, sitting, driving	Worse by static activities	Excess, possible blood stagnation
	Hot weather, pressure on the area	Worse by hot weather and pressure on the area	Heat, excess
	Any movement, everything	Non-specific	Excess
	After eating (-)*		Not able to classify
Pain alleviating factor	Reading, watching TV	Better by being distracted.	Not able to classify
	Cold packs, deep breathing, keeping busy	Better by cold packs, deep breathing, and keeping busy	Heat
	Hot weather, warm/hot bath	Better with heat	Cold
	Lying down, sleep	Better by rest	Deficient
	Sitting, pressure on the pain area	Better by sitting and applying pressure on the pain area	Deficiency
	Walking, gentle exercise	Better by gentle	Excess, possible

Domain	Factors	Factor names	Explanation
		movement	dampness
	Alcohol, nothing(-)*	Better with alcohol	Possibly Cold
	Any movement (-), pain killer	Better with pain killer	Not able to classify
	Bowel movement	Better with bowel movement	Excess
Other symptoms	Irritable, constipation, poor concentration, poor memory, low libido	Irritability, constipation, poor concentration, poor memory, and low libido	Deficiency, heat
	Distention sensation in the abdomen, heavy sensation in the body, mushy stools, abdominal distention	Abdominal distention and heavy sensation in the body.	Excess, possible dampness
	Cold hands and feet, thirsty, dry skin, dizziness	Cold extremity, thirsty, dry skin, and dizziness	Yin and Yang deficiency
	Cold joints, cold lower back or knees	Cold joints and back	Deficiency, cold
	Insomnia, frequent urination at night	Insomnia and frequent urination at night	Deficiency
	Short of breath, stuffiness in the chest	short of breath and stuffiness in chest	Excess or deficiency
	Feeling cold easily, poor appetite	Feeling cold easily and poor appetite	Deficiency, cold
	Red and hot joints, flushed face, hot palms	(Red and hot joints, palms, and face)	Excess, heat
	Night sweating, feeling tired easily	Night sweating and feeling tired easily	Deficiency, heat
	Indigestion, reflux	Upper digestive track issues	Excess
	Catch cold easily	Catch cold easily	Deficiency
	Limited movement, skin itch	Limited movement and skin itch	Heat

*(-) indicates a negative value. Symptoms with negative values mean the symptoms are related to the factor in the opposite way e.g. after eating (-) in pain aggravator means “after eating” does not aggravate pain.

7.3.3 Cluster analysis

The extracted factors were used for cluster analysis. The purpose for clustering the extracted factors is that factor analysis had reduced the 110 items into 36 factors and turned the dichotomous data into scale data, suitable for K-means cluster analysis. The ideal number of clusters was worked out from the hierarchical cluster analysis. Figure 7.5 shows the scree diagram derived from hierarchical cluster analysis. Figure 7.6 shows the enlargement of the elbow in the scree diagram to indicate the biggest change occurred in between stage 100 and 101. This left the ideal number of cluster to be six.

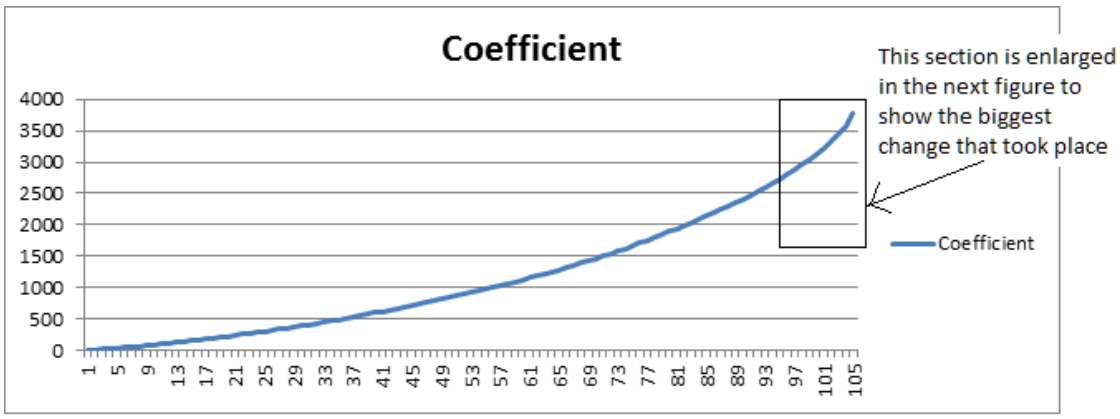


Figure 7.5 The scree diagram

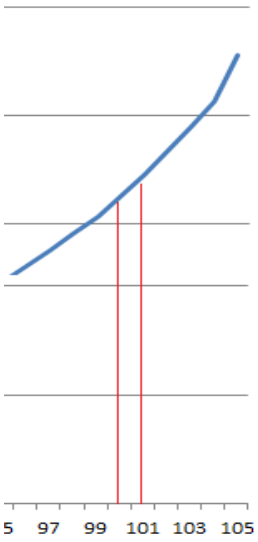


Figure 7.6 Enlargement of the elbow in the screen diagram

For K-means cluster analysis, the results are shown in Table 7.12. The numerical values shown in the table called “mean component values”, indicated how close the factor was to the centre of the cluster. A higher positive value meant a closer distance to the centre whereas a negative value meant being further away from that centre. For the purpose of the cluster analysis, only factors with positive mean component values are shown in Table 7.12 and are used for CM pattern identification as negative values mean the factors are away from the cluster and not relevant to that cluster.

Table 7.12 K-means cluster analysis

Final Cluster Centers						
	Cluster					
	1	2	3	4	5	6
Factor analysis - wk5 - pain quality – (hot and numb pain)	.29829	1.04774	.80616			.69329
Factor analysis - wk5 - pain quality – (dull pain at fixed location)		.01751	2.72487		.20410	
Factor analysis - wk5 - pain quality – (Sharp pain not dull with weakness)		.37981	1.99424	.17099		.13659
Factor analysis - wk5 - pain quality – (Dull pain)	1.67641				.08177	.44818
Factor analysis - wk5 - pain quality – (Sharp moving pain)	2.65148				.45325	
Factor analysis - wk5 - pain rhythm – (Pain fluctuates)	.72065	.52885			.03370	
Factor analysis - wk5 - pain rhythm - (Pain worse from morning to day time and better at night)		.80418	3.42520		.39928	
Factor analysis - wk5 - pain rhythm - (Pain better during the day and worse at all other times)	1.76002	.77478	1.55660			.66467
Factor analysis - wk5 - pain aggravating factor - (worse by exertion)	-.27440	.43277			.48314	
Factor analysis - wk5 - pain aggravating factor - (worse by mental strain)	1.47145		1.79819		.38195	.22826
Factor analysis - wk5 - pain aggravating factor – (Worse by both changing and wet weather)		1.13016	3.32095			.57361
Factor analysis - wk5 - pain aggravating factor - (worse by static activities)	1.45090		.35313		.09333	
Factor analysis - wk5 - pain aggravating factor – (Worse by hot weather and pressure on the area)		.65804				.96215
Factor analysis - wk5 - pain aggravating factor – (Non-specific)						.81479
Factor analysis - wk5 - pain aggravating factor - after eating (-)		.17352	.36801		.30087	
Factor analysis - wk5 - pain alleviating factor - (better by being distracted)	.91158	1.23911	.12683		.07232	.33069
Factor analysis - wk5 - pain alleviating factor – (Better by cold packs, deep breathing, and keeping busy)	.67441	.56013	1.13481			.63301
Factor analysis - wk5 - pain alleviating factor - (Better with heat)	.80873	1.03515	1.15941			.29660
Factor analysis - wk5 - pain alleviating factor - (Better by rest)	1.79373	.91922			.11952	.39746
Factor analysis - wk5 - pain alleviating factor – (Better by sitting and applying pressure on the pain area)			2.99475		.47626	.21762
Factor analysis - wk5 - pain alleviating factor - (Better by gentle movement)	1.31444			.11914		.16567

Final Cluster Centers						
	Cluster					
	1	2	3	4	5	6
Factor analysis - wk5 - pain alleviating factor – (Better with alcohol)	2.02484		.45418			.20925
Factor analysis - wk5 - pain alleviating factor – (Better with pain killer)		.02765			.26053	
Factor analysis - wk5 - pain alleviating factor – (Better with bowel movement)						1.74922
Factor analysis - wk5 - other symptoms - Irritability, constipation, poor concentration, poor memory, and low libido	.28826	.47026			.31340	.75921
Factor analysis - wk5 - other symptoms – (Abdominal distention and heavy sensation in the body)	3.26947	1.19612	2.94489			
Factor analysis - wk5 - other symptoms – (Cold extremity, thirsty, dry skin, and dizziness)		.49332			.21849	.16771
Factor analysis - wk5 - other symptoms – (Cold joints and back)		.01928	2.75338			.99611
Factor analysis - wk5 - other symptoms – (Insomnia and frequent urination at night)		.95164	2.48416			.23998
Factor analysis - wk5 - other symptoms – (short of breath and stuffiness in chest)			.41105		.05529	.55190
Factor analysis - wk5 - other symptoms – (Feeling cold easily and poor appetite)			.29106		.41435	
Factor analysis - wk5 - other symptoms – (Red and hot joints, face, and palms)	1.93445	.72705	.29451	.11181		.14420
Factor analysis - wk5 - other symptoms – (Night sweating and feeling tired easily)	1.75066				.16956	
Factor analysis - wk5 - other symptoms – (Upper digestive track issues)	2.61226		.39657			1.52161
Factor analysis - wk5 - other symptoms - catch cold easily	.42231				.22612	
Factor analysis - wk5 - other symptoms – (Limited movement and skin itch)	.30522	.54268		.08474		.42915

*To assist reading, negative values have been removed from the table.
Cells without any value means negative mean component value and is irrelevant to the cluster.

For CM patterns mentioned below, they were described from the CM perspective not western medicine perspective. Of the six clusters, cluster four (n=48) and cluster five (n=41) were the two largest groups whereas cluster one and three contained only one participant each, and cluster two (n=7) and cluster six (n=8) were also of a small number. Clusters one, two, three, and six were excluded from CM pattern identification here. Table 7.13 lists the contrast of cluster four and five. Cluster four contained less factors than cluster five. Cluster four presented with more of a heat related symptoms and cluster five presented with a more cold

related symptoms. The symptoms of these two presentations were opposite to each other such as hot joints and cold extremities. After reviewing cluster four and five, CM cluster analysis group researchers agreed that cluster four was of a CM heat pattern and cluster five was of a CM cold with deficiency pattern. It was agree by the CM cluster analysis group researchers that these two clusters are of opposite nature and cluster four presents with heat symptoms and cluster five presents with cold with deficiency symptoms.

Table 7.13 Contrast of cluster 4 and 5

Clusters	**Factors**				
	Pain quality	**Pain rhythm**	**Pain aggravator**	**Pain alleviator**	**Other symptoms**
Cluster 4	Sharp pain not dull with weakness	No symptom	No symptom	Better by gentle movement	Red and hot joints, palms, and face; Limited movement and skin itch
Cluster 5	Dull pain at fixed location; Dull pain; Sharp moving pain	Pain fluctuates; Worse during day time	Worse by exertion; Worse by mental strain; Worse by static activities; After eating (-)	Better by being distracted; better by rest; Better by sitting and applying pressure on the pain area; Better with pain killer	Irritability, constipation, poor concentration, poor memory, and low libido; Cold extremity, thirsty, dry skin, and dizziness; Short of breath and stuffiness in chest; Feeling cold easily and poor appetite; Night sweating and feeling tired easily; Catch cold easily

Each factor is separated by ;

For cluster four, the factors with positive mean component values are listed in Table 7.14. This cluster showed a heat type CM pattern with red and hot joints, flushed face, hot palms, and skin itch (Table 7.15).

Table 7.14 Cluster four with its factors (n=48)

Factors	Mean component value
Factor analysis - wk5 - pain quality - (Sharp pain not dull with weakness)	0.17099
Factor analysis - wk5 - pain alleviating factor - (Better by gentle movement)	0.11914
Factor analysis - wk5 - other symptoms – (Red and hot joints, palms, and face)	0.11181
Factor analysis - wk5 - other symptoms - (Limited movement and skin itch)	0.08474

Table 7.15 CM pattern and evidence for cluster four

CM pattern	Evidence
Heat	other symptoms – Red and hot joints, palms, and face, skin itch

For cluster five, the factors with positive mean component values are listed in Table 7.16 and the key signs and symptoms are listed in Table 7.17. This cluster of patients showed more of a cold with deficiency type CM pattern.

Table 7.16 Cluster five with its factors (n=41)

Factors	Mean component value
Factor analysis - wk5 - pain quality - (Dull pain at fixed location)	0.20410
Factor analysis - wk5 - pain quality – (Dull pain)	0.08177
Factor analysis - wk5 - pain quality - (Sharp moving pain)	0.45325
Factor analysis - wk5 - pain rhythm - (Pain fluctuates)	0.03370
Factor analysis - wk5 - pain rhythm - (Pain worse from morning to day time and better at night.)	0.39928
Factor analysis - wk5 - pain aggravating factor - (worse by exertion)	0.48314
Factor analysis - wk5 - pain aggravating factor - (worse by mental strain)	0.38195
Factor analysis - wk5 - pain aggravating factor - (Worse by static activities)	0.09333
Factor analysis - wk5 - pain aggravating factor - after eating (-)	0.30087
Factor analysis - wk5 - pain alleviating factor - (Better by being distracted)	0.07232
Factor analysis - wk5 - pain alleviating factor - (better by rest)	0.11952
Factor analysis - wk5 - pain alleviating factor – (Better by sitting and applying pressure on the pain area)	0.47626
Factor analysis - wk5 - pain alleviating factor – (Better with pain killer)	0.26053
Factor analysis - wk5 - other symptoms – (Irritability, constipation, poor concentration, poor memory, and low libido)	0.31340
Factor analysis - wk5 - other symptoms – (Cold extremity, thirsty,	0.21849

Factors	Mean component value
dry skin, and dizziness)	
Factor analysis - wk5 - other symptoms – (short of breath and stuffiness in chest)	0.05529
Factor analysis - wk5 - other symptoms – (Feeling cold easily and poor appetite)	0.41435
Factor analysis - wk5 - other symptoms – (Night sweating and feeling tired easily)	0.16956
Factor analysis - wk5 - other symptoms - catch cold easily	0.22612

Table 7.17 CM pattern and evidence for cluster five

CM pattern	Evidence
Cold	Other symptoms - short of breath, stuffiness in the chest, low libido, cold hands and feet, feeling cold easily, poor appetite.
Deficiency	Pain rhythm - "worse during the day, better at night" Pain aggravating factor - (worse by exertion) Pain alleviating factor - (better by rest), (Better by sitting and applying pressure on the pain area) Other symptoms - poor concentration, poor memory, low libido, cold hands and feet, dizziness, (Feeling cold easily and poor appetite), (Night sweating and feeling tired easily), catch cold easily

7.3.4 CMP clusters, their demographic difference(s), and their pain related data

7.3.4.1 CMP clusters and their demographic data

For clusters with more than one participants (cluster two, four, five, and six), they were compared for their age using ANOVA. There was no statistically significant difference between groups in age distribution (Table 7.18).

Table 7.18 Comparison of demographic group data (ANOVA) (n=103)

Dependent Variable	Cluster	n	Mean	Std. Error	95% Confidence Interval		ANOVA		
					Lower Bound	Upper Bound	F	df	Sig
Age	2	7	46.1429	8.05170	26.4410	65.8447	1.424	3	0.240
	4	48	55.6042	1.89314	51.7957	59.4127			
	5	41	55.7805	2.07468	51.5874	59.9736			
	6	7	60.4286	2.75903	53.6775	67.1797			

For the Chi square test on other demographic data, including gender, country of birth, marital status, education background, and current work status, there was no significant difference between the four clusters after taking Bonferroni correction and set α level at 0.0083 (Table 7.19).

Table 7.19 Comparison of cluster demographic data

Demographic variable	CMP clusters	Missing	male	female	Total N	Pearson Chi square		
						value	df	Asymp sig (2-sided)
Gender	2	0	2	5	7	2.706	3	0.439
	4	0	25	23	48			
	5	0	17	24	41			
	6	0	2	5	7			
Marital Status	CMP clusters	Missing	Married/de facto	Single/separated/divorced/widow				
	2	0	1	6	7	4.847	3	0.183
	4	1	27	20	48			
	5	1	19	21	41			
	6	0	3	4	7			
Education	CMP clusters	Missing	year 12 and above (include university, adult education CAE, TAFE, and HSC)	Under year 12	Other			
	2	1	2	4	0	4.939	6	0.552
	4	1	31	16	0			
	5	2	22	16	1			
	6	0	3	4	0			
Current work status	CMP clusters	Missing	employed (including full/part time working, and voluntary work)	unemployed (including home duties, student, unemployed due to pain, retraining, and unemployed due to other reasons)	retired			
	2	1	2	3	1	4.778	6	0.573
	4	1	5	27	15			
	5	2	5	26	8			
	6	0	1	3	3			
Country of birth	CMP clusters	Missing	North Africa and Middle East	North West Europe	Oceania	South East Asia	Southern and Eastern Europe	Sub-Sahara Africa
	2	0	0	0	5	0	2	0	7	13.627	18	0.753
	4	1	1	10	31	0	3	2	48			
	5	2	2	4	27	1	4	1	41			
	6	0	0	2	3	0	2	0	7			

HSC: High School Certificate
CMP: Chronic musculoskeletal pain

7.3.4.2 CMP clusters and their pain related data

Pain related data were compared among clusters. They included 1) Years in pain, 2) Total pain regions at baseline week, 3) average of OM consumption of baseline weeks, 4) average of NonOM analgesics of baseline weeks, 5) average of highest pain of baseline weeks, 6) average of average intensity of baseline weeks, 7) unpleasantness of pain of average of baseline weeks, 8) RMDQ, 9) total score of BDI at baseline week, 10) physical health total of SF36 at baseline week, 11) mental health total of SF36 at baseline week, and 12) total SF36 score at baseline week. MANOVA showed statistical differences between them (Wilk's Λ=0.540, F(36, 231.187) = 1.489, p=0.044, partial $\eta 2$=0.186). Separate ANOVA showed statistical significant difference in years in pain (F(3,89) = 4.730, p=0.004, partial $\eta 2$=0.138) after adjusted for Bonferroni's correction and taking α level at 0.05/12=0.00417) (Table 7.20). Cluster four had the shortest years in pain (M: 10.140) whereas cluster six had the longest years in pain (M: 24.714)

Table 7.20 MANOVA of clusters and pain related data at baseline week(s) (n=104)

Multivariate Tests[a]							
Effect		**Value**	**F**	**Hypothesis df**	**Error df**	**Sig.**	**Partial Eta Squared**
Intercept	Pillai's Trace	0.974	241.434[b]	12.000	78.000	0.000	0.974
	Wilks' Lambda	0.026	241.434[b]	12.000	78.000	0.000	0.974
	Hotelling's Trace	37.144	241.434[b]	12.000	78.000	0.000	0.974
	Roy's Largest Root	37.144	241.434[b]	12.000	78.000	0.000	0.974
Clusters	Pillai's Trace	0.531	1.432	36.000	240.000	0.061	0.177
	Wilks' Lambda	0.540	1.489	36.000	231.187	0.044	0.186
	Hotelling's Trace	0.727	1.548	36.000	230.000	0.031	0.195
	Roy's Largest Root	0.512	3.414[c]	12.000	80.000	0.000	0.339
a. Design: Intercept + Clusters							
b. Exact statistic							
c. The statistic is an upper bound on F that yields a lower bound on the significance level.							
Tests of Between-Subjects Effects							
Source		**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**	**Partial Eta Squared**
Clusters	Years in pain	1517.352	3	505.784	4.730	0.004 *	0.138
	Total pain region	97.334	3	32.445	0.953	0.419	0.031
	Average of OM consumption	554606.154	3	184868.718	0.657	0.581	0.022
	Average of NonOM	56.194	3	18.731	0.386	0.763	0.013

	analgesics						
	Average of highest pain intensity	10.113	3	3.371	1.208	0.312	0.039
	Average of average pain intensity	19.916	3	6.639	1.905	0.134	0.060
	RMDQ	177.231	3	59.077	1.766	0.159	0.056
	Average unpleasantness of pain	53.260	3	17.753	2.457	0.068	0.076
	Total score of BDI	1063.787	3	354.596	2.867	0.041	0.088
	Physical health total of SF36	2241.621	3	747.207	3.324	0.023	0.101
	Mental health total of SF36	4682.483	3	1560.828	4.052	0.009	0.120
	Total SF36 score	3407.135	3	1135.712	3.914	0.011	0.117

Final 6 clusters using K means

Dependent Variable	Cluster	n	Mean	Std. Error	95% Confidence Interval	
					Lower Bound	Upper Bound
Years in pain	2	7	18.800	4.625	9.611	27.989
	4	48	10.140	1.577	7.006	13.273
	5	41	14.105	1.678	10.772	17.438
	6	8	24.714	3.908	16.948	32.480
Total pain region	2	7	10.200	2.610	5.014	15.386
	4	48	7.791	0.890	6.022	9.559
	5	41	7.895	0.947	6.014	9.776
	6	8	11.286	2.206	6.903	15.668
Average of OM consumption	2	7	511.013	237.241	39.621	982.405
	4	48	414.761	80.898	254.017	575.504
	5	41	544.185	86.056	373.193	715.177
	6	8	657.983	200.505	259.584	1056.383
Average of NonOM analgesics	2	7	13.035	3.115	6.846	19.224
	4	48	10.124	1.062	8.014	12.235
	5	41	9.919	1.130	7.674	12.164
	6	8	11.607	2.633	6.376	16.838
Average of highest pain intensity	2	7	5.466	0.747	3.981	6.950
	4	48	6.604	0.255	6.098	7.111
	5	41	6.058	0.271	5.519	6.596
	6	8	6.552	0.631	5.297	7.807
Average of average pain intensity	2	7	3.949	0.835	2.290	5.607
	4	48	5.669	0.285	5.104	6.235
	5	41	4.969	0.303	4.367	5.570
	6	8	5.630	0.706	4.228	7.031
RMDQ	2	7	14.000	2.586	8.861	19.139
	4	48	10.698	0.882	8.945	12.450
	5	41	12.632	0.938	10.767	14.496
	6	8	15.143	2.186	10.800	19.486

Average unpleasantness of pain	2	7	10.343	1.202	7.954	12.732
	4	48	12.537	0.410	11.722	13.351
	5	41	11.216	0.436	10.350	12.083
	6	8	12.821	1.016	10.803	14.840
Total score of BDI	2	7	23.200	4.974	13.317	33.083
	4	48	16.465	1.696	13.095	19.835
	5	41	23.474	1.804	19.889	27.059
	6	8	21.571	4.204	13.219	29.924
Physical health total of SF36	2	7	29.240	6.705	15.917	42.563
	4	48	37.172	2.286	32.629	41.715
	5	41	27.168	2.432	22.336	32.001
	6	8	27.114	5.667	15.854	38.374
Mental health total of SF36	2	7	38.187	8.777	20.746	55.627
	4	48	52.310	2.993	46.363	58.257
	5	41	37.609	3.184	31.282	43.935
	6	8	41.552	7.418	26.812	56.292
Total SF36 score	2	7	32.142	7.618	17.005	47.278
	4	48	44.880	2.598	39.718	50.041
	5	41	32.598	2.763	27.107	38.088
	6	8	34.149	6.438	21.356	46.942

* significant difference
BDI: Beck Depression Inventory
OM: Opioid medication
RMDQ: Roland Morris Disability Questionnaire
SF36: Medical Outcome Short Form Health Survey 36 items.

7.4 Discussion

The aims of this chapter were to 1) establish the CM pattern(s) for CMP patients who use OM for pain control by using the clinical data gathered by CMPQ at the baseline stage of the clinical trial; and 2) identifying any possible differences in the demographic data and feature of pain among the clusters.

Through factor and cluster analysis, the current study identified two key patterns of CMP sufferers who consumed OM for pain control and provided their CM pattern diagnosis. The two patterns are a CM heat type pattern and a CM cold with deficiency type pattern. The CM heat type pattern presented with red and hot joints, face, and palms, and itchy skin. These symptoms in CM are due to heat in the body [1025(p658)]. And the CM cold with deficiency type pattern presented with short of breath, stuffiness in the chest, low libido, cold extremities, feeling cold easily and poor appetite as well as pain aggravated by exertion, better by rest, applying pressure on the area, poor concentration, poor memory, night sweating, feeling tired easily. These are due to cold and deficiency in CM understanding [38].

7.4.1 Factor analysis

The purpose of using factor analysis was to reduce variables into small subset of factors based on their variance [1057]. The purpose of cluster analysis was to group similar symptoms in a large multivariate data set [1016,1058]. Using factor analysis to reduce variables and then using cluster analysis to group the factors had been used before [1059,1060]. This study is an exploratory study where there is no predefined number of clusters or factors and utilised the factor analysis then cluster analysis approach. This study utilised SPSS to reduce the 110 variables down to 36 factors and further clustered them into six clusters

During the process, the factors extracted met the minimum KMO value (0.5) and the aggravating factors reached good KMO value (>0.7). Except for the domain of pain rhythm, other domains were all meeting the minimum of or almost 60% total variance explained for the factor analysis. And for the cluster analysis, K-means, which was appropriate for scale data only, was used as factor analysis had turned the dichotomous data into scale data factors which was suitable for K-means cluster analysis. Of the factors, they have all been rotated with varimax method except for pain quality. The statistician (A/Prof Da Costa) advised to attempt different ways in SPSS for a meaningful data output. This approach, not to rotate the pain quality, was then adopted as when pain quality symptoms were extracted and rotated, the symptoms of cold and heat were grouped in the same factor. Such result would make the interpretation of clusters difficult if not impossible. It was necessary to separate the heat and cold symptoms in order to derive interpretable CM patterns.

7.4.2 CM patterns: heat and cold patterns

Of the clusters, the case distribution was not even amongst the different clusters. Only the CM patterns of the two biggest clusters were identified based on the CM eight guiding principles. Most of the participants had a “heat pattern” (cluster four, n=48), followed by a “cold with deficiency pattern” (cluster five, n=41). This indicates there are two distinctive CMP sub types. The heat pattern is “Yang, interior, heat, with uncertainty in deficiency/excess”, the uncertainty in deficiency/excess comes from no other signs and symptoms to further support deficiency/excess. The cold with deficiency pattern is “Yin, interior, cold, and deficiency”, and is supported with signs and symptoms that reflect features of combined cold and deficiency patterns.

In CM, CMP may be due to blockages or deficiency. Blockages are considered to be an excessive patterns and deficiency a deficient pattern. The blockage due to excess may be by exterior pathogens (such as cold, heat, and dampness), Qi stagnation and blood stasis, phlegm stagnation. On the other hand Qi and blood deficiency, or Yin essence depletion, and malnourishment of the organs and meridians can also cause pain due to deficiency [1019(p305)].

Table 7.21 lists the comparison between the two patterns in their aetiology, pathogenesis, signs and symptoms, treatment principles and possible treatments in CM perspective. In CM, the heat pathogen is a Yang pathogen, it dries up the Yin essence and blood in the body whereas the cold pathogen is a Yin pathogen, cold pathogen obstructs the movement of Qi and blood and consumes Yang Qi of the body. Both pathogens cause pain to occur eventually (Figure 7.7). It is uncertain what the exact causes of heat patterns and cold with deficiency patterns are as this study did not specifically enquire into the onset of participants' pain. It may have been CMP patients consumed hot/cold property substances, exposed to heat/cold pathogens/factors for long term which caused either heat or cold to form. Based on the side effects of OM, which include sedation [1061], dizziness [1061], nausea [1061], vomiting [1061], constipation [1061], physical dependence [1061], tolerance [1061], respiratory depression [1061], night sweating [1062], and excessive sweating [1063], some of them can be attributed to the heat symptoms [38], e.g. constipation; some of them can be attributed to the cold and/or deficiency symptoms [132(p64,67)], e.g. dizziness, nausea, and vomiting; and sweating can be either heat or deficiency symptom depending on the accompanying symptoms [38]. Traditionally, opium ("ying su ke" in Chinese pinyin), the raw plant where OM is derived from, is sour, neutral, astringent, and toxic, which is used to treat diarrhoea, long term cough, rectal prolapse, and alleviating pain [1064(p1045)]. According to the function of opium, it may be patients consumed OM which astringed the heat or cold pathogens inside the body and caused the accumulation of them. Subsequently patient presented with all these symptoms of cold or heat as opioids may aggravate the symptom that individual patient has. Hence when patients discontinued OM, their bowel movement is no longer astringed and their constipation then improved [1061]. As illustrated in Figure 7.7, whether heat or cold pattern is developed, after consuming OM, depends on the pre-existing condition of individuals. And these two CM patterns inform of no cause of the cold or heat. Treatments for cold or heat pattern also differ significantly in their treatment principle and methods of treatment (Table 7.21). The use of moxibustion is often recommended for pain with a cold and deficient pattern, but discouraged for the heat pattern [147(p56)].

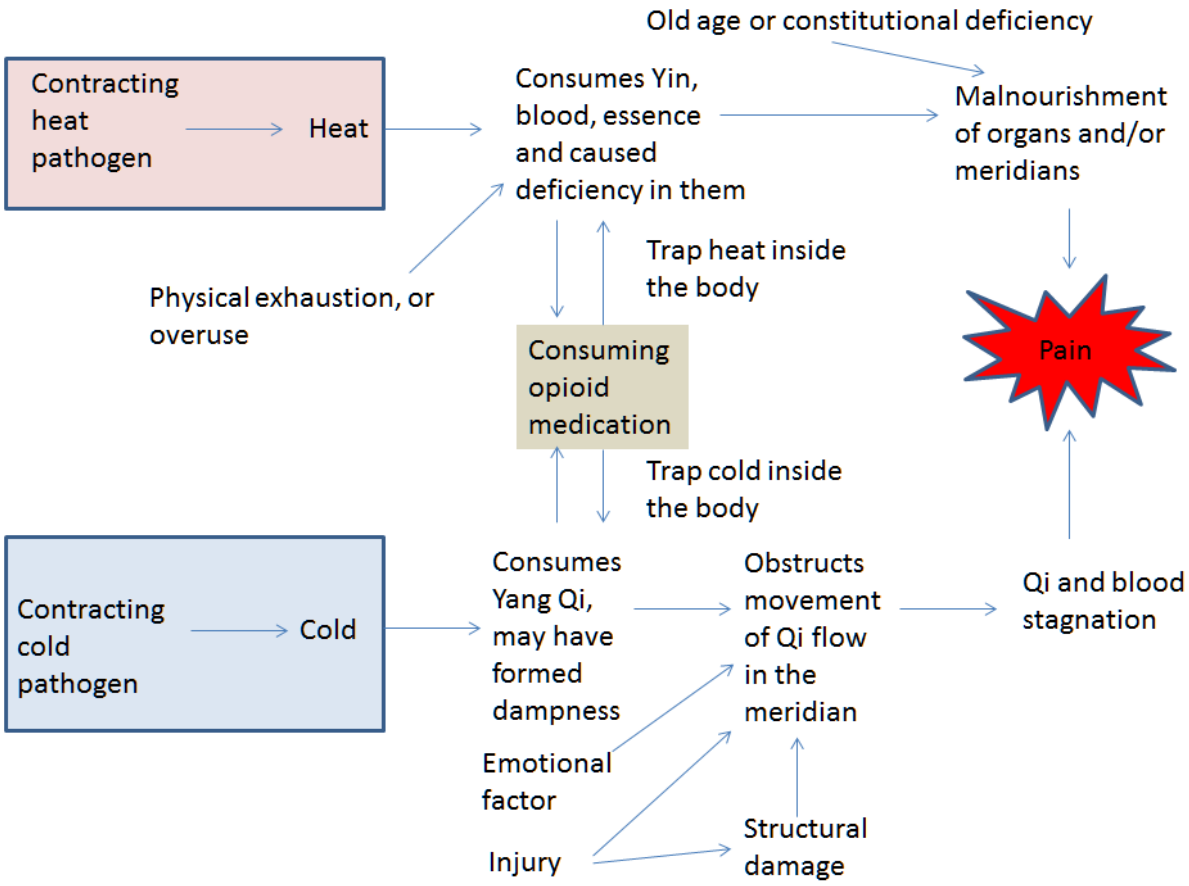


Figure 7.7 Diagram explaining how cold and heat patterns may have formed and how opioids might contributes to the process

Table 7.21 Contrasting aspects of the two patterns

	CM heat pattern	**CM cold with deficiency pattern**
Possible Aetiology	Contracting heat pathogen, or cold and dampness pathogens which lingered and turned into heat. Chronic consumption of heat substance, including consuming medication which stimulates a person e.g. stimulants.	Contracting cold pathogen, overuse, constitutional deficiency, physical exhaustion, old age, and chronic consumption of cold substance, including medication which calms the person e.g. sedatives.
	These aetiologies do not exclude injury, over use or other factors as causes. More information is required to ascertain the cause of pain.	
Pathogenesis	The heat pathogen/substance caused heat to accumulate internally.	The cold pathogen accumulates and damages Yang Qi of the body. Over use, physical exhaustion, constitutional deficiency, and old age lead to deficiency. Consumption of cold substance, causes the

	CM heat pattern	CM cold with deficiency pattern
		cold pathogens to accumulate in the body and damages the Yang Qi.
Signs and symptoms	Red and hot joints, palms, and face, skin itch	Cold - short of breath, stuffiness in the chest, low libido, cold hands and feet, feeling cold easily, poor appetite. Deficiency – Pain "worse during the day, better at night", (worse by exertion), (better by rest), (Better by sitting and applying pressure on the pain area) Other symptoms - poor concentration, poor memory, low libido, cold hands and feet, (Feeling cold easily and poor appetite), (Night sweating and feeling tired easily), catch cold easily
Treatment principal	Clear heat and stop pain	Tonify Yang Qi, expel cold, and stop pain
Treatments	Acupuncture, Chinese herbal medicine, diet change, life style advices.	Acupuncture, moxibustion, Chinese herbal medicine, diet change, life style advices, Tuina (Chinese therapeutic massage).

In comparison with the textbook information on CM diagnosis, the current study found CMP mainly due to heat or “cold with deficiency” patterns but not the other patterns as listed in Table 7.22. It may be due to the items generated were based on the CM eight guiding principles and not Zang Fu diagnosis, the complexity of CMP, and the lack of inspection and palpation data. Subsequently only simple diagnosis can be derived. It may also be the sample size was small and only allowed for two main patterns to manifest.

Table 7.22 CMP CM patterns as listed in the CM textbooks

Text	Conditions	CM patterns
Chinese medicine orthopedics and traumatology textbook [1022] (p963,973,976,984,987,995,996,1002,1005,1007,1012,1014,1017,1019,1023,1032,1034,1042,1045,1047,1051,1054,1062,1069,1078,1094,1097,1107,1108,1116,1131,1136,1158,1168,1171,1172,1176,1177,1306,1325,1536,1538,1541-1548,1554-1557,1567-1570,1574-1576,1579-1581,1583,1584,1586-1588	Various types of CMP	Excessive type: cold dampness, cold damp Bi retention, wind cold, wind cold Bi stagnation, wind cold dampness, wind dampness blocking the vessel, damp heat retention inside, CM liver Yang upsurge, turbid phlegm stagnates in middle Jiao
		Static and stagnant type: Qi stagnation and blood stasis, Qi stagnant type, blood stasis type
		Deficient type: CM liver and CM kidney deficiency/insufficiency, Qi and blood deficiency, CM kidney deficiency type, CM kidney Qi deficiency, deficient cold

Text	Conditions	CM patterns
,1631-1635,1642-1644,1650-1651,1652-1653,1654-1656)		
Internal medicine of Chinese medicine [132] (p706-708,890-895)	Low back pain	Excessive type: cold dampness Bi obstruction, damp heat obstruction
		Static and stagnant type: blood stasis, Qi stagnation
		Deficient type: CM spleen deficiency, and CM kidney deficiency
	Bi syndrome (blockages of Qi and blood flow in the muscles, joints, bones, and tendons)	Excessive type: wind dampness Bi obstruction, cold dampness Bi obstruction, mixture of cold and heat, damp heat Bi obstruction, heat toxin Bi obstruction
		Static and stagnant type: blood stasis Bi obstruction, phlegm dirt Bi obstruction, phlegm stasis Bi obstruction
		Deficient type: Qi and Yin (blood) both deficient, CM liver and CM kidney both deficient

* Bi means pain in CM

During the course of differentiating the CM patterns of CMP patients, there were some symptoms that could not be explained by the two CM patterns (Table 7.23). Pain relieved by pain killer and limited movement are not explainable in CM. Other symptoms can be classified into Qi stagnation, blood stasis, dampness retention, Yin and/or Yang deficiency which can all be secondary to the consequences of cold and heat. In CM, dampness is a Yin pathogen that can slow down the movement of Qi and consumes Yang. It is not a surprise finding within the study that many participants present with the symptoms of Qi stagnation, blood stasis, dampness retention, Yin and/or Yang deficiency. It is normal in CM practice that not all symptoms are explained by the pattern. But it is important to identify the main symptoms which reflect the main pattern and not to focus on the irrelevant symptoms [1019(p818)].

Table 7.23 Symptoms not explainable by the two CM patterns

Domains	Heat pattern	Cold with deficiency pattern
	Symptoms	
Pain quality	Sharp pain not dull with weakness	Pain at fixed location; Sharp moving pain
Pain rhythm	No symptom	Pain fluctuates
Pain alleviating factor	Better by gentle movement	Better by being distracted; Better with pain killer
Pain aggravating factor	No symptom	Worse by static activities
Other symptoms	Limited movement	Irritability, constipation, thirsty, dry skin

In CM, there is also a diagnosis based on Zang Fu (脏腑) organs. Fu (腑) organs mean the hollow organs, e.g. large/small intestines (大/小肠), gallbladder (胆), urinary bladder (膀胱), stomach (胃), and San Jiao (三焦) which means the invisible water passage, and the Zang (脏) organs are solid organs, e.g. heart (心), lung (肺), spleen (脾), kidney (肾), pericardium (心包), and liver (肝). As list in Table 7.22, the organs involved with CMP are CM kidney, CM liver, and CM spleen 1022(p963,973,976,984,987,995,996,1002,1005,1007,1012,1014,1017,1019,1023,1032,1034,1042,1045,1047,1051,1054,1062,1069,1078,1094,1097,1107,1108,1116,1131,1136,1158,1168,1171,1172,1176,1177,1306,1325,1536,1538,1541-1548,1554-1557,1567-1570,1574-1576,1579-1581,1583,1584,1586-1588,1631-1635,1642-1644,1650-1651,1652-1653,1654-1656)132(p706-708,890-895). In addition, there is a famous CM phrase “all kinds of pain, ulcers, pruritus all belong to heart” (诸痛疮痒皆属于心) which indicates the involvement of CM heart organ. Chinese medicine lung and other hollow organs are not involved in CMP. Of these organs CM kidney has the direct connection with low back region and is most closely associated with LBP [130]. According to another clinical study by MacPherson et al., of the 148 LBP patients, the only key Zang Fu organ diagnosis by the practitioners was CM kidney deficiency [1065]. Another study looked at CM pattern diagnosis for osteoporosis [1050]. Their Zang Fu organ diagnosis was different from MacPherson et al. [1065] and focused on CM kidney, CM liver, and CM spleen. In CM, apart from low back region, the other anatomical regions are not related to any organs. Although there is the involvement of CM liver and CM spleen, their involvements in anatomical regions are very limited. Chinese medicine liver and hypochondriac region (the lower rib area) are related. Chinese medicine spleen dominates the four limbs. The hypochondriac region is not commonly involved in CMP. In this sample, only 8.5% of participants had pain in side of the body and only 15.1% of participants have pain in the chest region. Although CM spleen dominates the four limbs, where in the four limbs was not clearly explained in CM theory. Thus it is not practical to use Zang Fu diagnosis in CMP and both textbooks and clinical studies did not involve CM lung organ in CMP.

In comparison with other CM pattern identification studies (Table 7.24), Berle et al. researched in CM pattern by looking at how many symptoms a hepatitis C patient is suffering then divides the number of symptoms by the total number of symptoms of a specific CM pattern. Then a patient is given a percentage of a specific CM pattern [1066]. For example, a patient experiences eight symptoms out of 11 symptoms of CM liver Yin deficiency and at the same time also experiences six symptoms out of nine symptoms of CM liver Qi stagnation.

Then this patient is diagnosed with 73% of CM liver Yin deficiency and 67% of CM liver Qi stagnation. Such approach is not utilized in the current study as the current study intends to find out the primary CM patterns using the CM eight guiding principles rather than the individualized types of CM pattern with a pre-defined list. MacPherson et al. looked into CM pattern of LBP and involved six practitioners to diagnose the patients [1065]. The CM patterns for LBP are Qi and blood stagnation (70%), Bi syndrome (9%), and CM kidney deficiency (18%) based on the primary analysis. MacPherson's approach is using practitioner to diagnose the patient and select the pre-defined patterns with pre-defined key symptoms for each pattern. This project differs from the two studies by utilizing questionnaire to collect the data without pre-defined pattern and without pre-defined key symptoms for CM patterns. And this project utilized statistical methods to group the symptoms together instead of the practitioners to collect and diagnose the patients, making the symptom grouping more objective [1067].

Table 7.24 Comparison of different approach to pattern identification

	Current project	**Berle et al. [1066]**	**Macpherson et al. [1065]**
Participants	106 CMP patients who use OM for pain control	16 Hepatitis C participants	148 LBP patients
Method of pattern identification	Using scientific sound factor analysis and cluster analysis	List of symptoms extracted from literatures for the 17 identified CM patterns	Pre-defined list of pattens with key symptoms
Method of pattern interpretation	By the CM cluster analysis group researchers	Each of the 17 CM patterns had its own list of symptoms. By dividing the number of presenting symptoms by the total number of symptoms in the pattern. Patients are diagnosed as A% of B pattern and C% of D pattern depending on how many symptoms patients present with.	By practitioners ticking on the pre-defined list of patterns.

CM: Chinese medicine
CMP: Chronic musculoskeletal pain
LBP: low back pain

7.4.3 Differences in pain measures among CM patterns

For the different clusters, after taking Bonferroni correction into consideration ($\alpha = 0.00417$), only duration of pain showed significant difference between the four clusters. Cluster four had the shortest duration of pain and cluster six had the longest duration of pain. Only cluster four

(n=48) had the significant larger sample size than cluster six (n=8). Comparing their symptoms, cluster six's symptoms were more complicated than cluster four and actually had all of cluster four's symptoms (Table 7.25). It may be cluster six is the advanced version of cluster four and is understandable to be having a longer pain history.

Apart from symptom presentation, Zhou et al. and Lu et al. researched into the molecular signature and gene expression of the heat and cold pattern of RA patients [1068,1069]. In one study, Zhou et al. recruited 33 female RA patients, of which 12 had heat pattern and 21 had cold pattern, and 12 healthy volunteers [1068]. The author had found the genes related to the up-regulation of cell proliferation, the EIF4A2, CCNT1, and IL7R and the Jak-STAT cascade, were highly related to the CM cold pattern of RA. The genes related to the fatty acid metabolism, the PRKAA1, HSPA8, and LSM6, and the I-κB kinase/NF-κB cascade, were highly related to the CM heat pattern of RA. In another study [1069], Lu et al. recruited 10 RA patients with heat pattern and 10 RA patients with cold pattern and analysed their blood with microarray technology to reveal the gene expression profiles in CD4+ T cells. The author had found 29 genes important in differentiating cold and heat patterns. The cold pattern is closely associated with seven of them. This indicates the cold and the heat patterns not only differ in the symptom presentation, they also differ in the molecular signature and gene expression. This warrants further research into the subgroups of diseases.

Table 7.25 Comparison of signs and symptoms of cluster four and six

Domain	Cluster four	Cluster six
Pain quality	**Sharp pain not dull with weakness**	**Sharp pain not dull with weakness;** Dull pain; hot and numb pain;
Pain rhythm	No symptom	Pain better during the day and worse at all other times
Pain aggravator	No symptom	worse by mental strain; worse by both changing and wet weather; worse by hot weather and pressure on the area; non-specific
Pain alleviator	**Better by gentle movement**	**Better by gentle movement;** Better by being distracted; better by cold packs, deep breathing, and keeping busy; better with heat; better by rest; better by sitting and applying pressure on the pain area; better with alcohol; better with bowel movement
Accompanying symptoms	**Red and hot joints, palms, and face; limited movement and skin itch**	**Red and hot joints, face, and palms; limited movement and skin itch;** Irritability, constipation, poor concentration, poor memory, and low libido; cold extremity, thirsty, dry skin, and dizziness; cold joints and back; insomnia and frequent urination at night; short of breath and stuffiness in chest; upper digestive track issues;

Each factor is separated by ;
Bold indicates common symptoms amongst the two clusters and are place at the beginning of each cell.

Limitations of the study:

1) Not all types of CMP were included, mainly pain in the back, neck, hip, and knee. Other types of CMP may include tennis elbow, frozen shoulder, repetitive strain injury, arthritis of hands.

2) Tongue and pulse data were not used in the diagnosis as they require a practitioner to obtain such data but the questionnaire is designed to be completed by patients themselves.

3) Used a convenient sample of a subgroup of CMP who used OM for pain control.

Although not all types of CMP were included, pain in the lower back (77.4%), neck (45.3%)), hip (43.4%), and knee (40.6%) are frequently occurring [1070,1071] and are considered as diseases

of priority according to WHO [1072]. Although the study only focused on the subgroup of CMP who use OM for pain control, this particular group is a specific group of moderate to strong pain [1073], and 13% of chronic pain patient used OM [1074]. Literature suggested the minimum of 50 subjects for exploratory factor analysis [1075]. Providing 106 subject data is more than needed for an exploratory factor analysis.

Implication for clinical practice

The current study has identified the two major types of CM pattern of CMP who use OM for pain control – heat type and cold with deficiency type. This could guide clinical practice. For instance for cold pattern, moxibustion should be added to provide warmth; while for the heat pattern, the application of moxibustion or a heat lamp should be minimal or not utilised. The current study provides a pattern identification reference for this particular subgroup of CMP. Caution is advised when extrapolating the CM pattern to CMP sufferers who have pain other than lower back, neck, hip, and knee areas as not many of them, especially upper limb regions, were included in the study.

Implication for future research

Factor analysis and cluster analysis can provide a statistical means to group symptoms and can be recommended for future CM pattern research. More CM pattern researches on CMP other than CMP who use OM are also recommended to further understand CMP. Chinese medicine eight guiding principles is easy to apply for pattern identification. It can be used for CM pattern identification research of other health conditions.

Two main patterns of CMP who use OM for pain control had been identified in this chapter. Their differences had been examined and their CM patterns had been diagnosed. The next chapter will focus on effect of EA on the participants as well as the patterns. Differences amongst the two major patterns were also examined using BDI, SF36, OM consumption, and pain intensity.

8. EFFECT OF TREATMENT ON PATTERNS AND SYMPTOMS (SUB-GROUP) AND ASSOCIATION BETWEEN SUB-GROUP AND OTHER OUTCOME MEASURES

8.1 Introduction

The common questionnaires or outcome measures for acupuncture research in pain include VAS for pain, daily OM consumption, SF36 for QoL, BDI for depression, and RMDQ for pain related disability. These specific areas measured may not be exactly the most adequate ones to reflect the holistic effect of acupuncture. As described in Chapter 2.6 Chinese medicine (p. 32), CM views the body holistically, where body parts and medical conditions are related to one another via CM's theories, and there are different patterns in the view of CM within one western medicine diagnosis, for instance osteoarthritis. When arthritis comes with fatigue and weakness, this is a deficient type pattern, and when arthritis comes with pain refused to be touched, this is an excess type pattern.

Clinically, after acupuncture treatment, patients may have improvement in sensitivity to a stimulus (e.g. heat and/or cold), in the rhythm of the symptom (e.g. pain all the time, pain only occurs in the evening), pain quality (e.g. pain at a fixed location, sharp pain sensation, pain that moves around). Apart from pain, acupuncture had also been used to improve sexual functioning (e.g. libido) [1076], and digestion (e.g. abdominal distention) [1077]. According to the text book of acupuncture Shu Xue Xue [腧穴学], the point LI4 (He Gu, 合谷) can be used for a wide range of symptoms including problems of head, eye, nose, teeth, jaw, ear, throat, cough, vertigo, sweating, epigastric and abdominal pain, constipation, dysentery, amenorrhoea, and difficult child labour, hypertension, skin itchiness, urticaria [144(p86)]. Such effects are not necessarily captured in acupuncture trials unless the authors specifically asked questions related to these aspects. Researchers have argued that when assessing the effectiveness of acupuncture in fibromyalgia patients, sleep and cognitive function should be assessed as those symptoms may be ameliorated in this group of patients due to the holistic effects of acupuncture [1078]. And according to the findings from Chapter 3.3.6 Summaries for comorbidities/accompanying symptoms of CMP (p. 124), CMP is often accompanied with headache (OR 1.33-7.0), hypertension (OR 1.5-2.9), and digestive ulcer (OR 3.1-4.0). Unless the treating doctor specifically asks for questions related to headache, hypertension, or epigastric pain, it is likely the doctor is going to miss the changes in related symptoms or

signs when he/she treats the CMP patient by needling LI4. It is important to capture and evaluate the symptom presentation in CM way in order to evaluate the broader effect of acupuncture before and after acupuncture treatments. The current CMPQ can capture these changes before and after acupuncture treatment. For the CM heat pattern and CM cold with deficiency pattern identified in Chapter 7.3.3 Cluster analysis (p. 236), it was uncertain which one of them was associated with better/worse QoL, mild/severe depression/pain, or more/less OM consumption, and which one of the CM patterns responded better to REA for QoL, OM reduction, depression, and pain.

The CMPQ developed in Chapter 6 Initial development of CMPQ (p. 184) was for both the diagnostic and outcome assessment purposes. It assesses the outcome by asking patients if they had experienced such symptoms. By repeated measurements, a CM doctor can know if there is a change in patients' symptoms. Based on the symptoms patients ticked, the CM doctor can diagnose a CM pattern for the condition. By examining the changes in the number and types of symptoms, the CM doctor can make an estimate on if the patient is improving and on which aspect the improvement has happened.

The four aims of this chapter were to test

- Aim one: To identify the group difference between the CM "heat" and "cold with deficiency" patterns.
    - Objective one: If there are differences between CM "heat" and "cold with deficiency" patterns in "average pain intensity" and "average OM consumption" at baseline weeks, or BDI and SF36 at baseline week.
- Aim two: If CMPQ could be used to assess changes after treatment and if the three treatment groups induced different changes in CMPQ.
    - Objective two: if CMPQ could capture changes in signs and symptoms on participants who use OM for CMP after REA, SEA, or PMM alone treatment.
- Aim three: if the CM "heat" or "cold with deficiency" patterns differed in REA

treatment response

    - Objective three: If it is possible to identify the CM pattern with the best improvement after REA treatment based on the symptoms in CMPQ.

- Aim four: if the CM "heat" or "cold with deficiency" patterns responded differently to treatments in pain, OM consumption, QoL, and depression.

    - Objective four: if there is any CM pattern responding to treatments better as assessed with "average pain intensity" and "average OM consumption" at the end of treatment weeks, QoL and depression at the end of treatment week.

8.2 Methods

8.2.1 Participants

Participant identification and recruitment were described in Chapter 4.2 Initial development of CMPQ (p. 141). Briefly participants had to take OM and suffered from CMP. Participants were identified from hospital case record from both Caulfield pain management and research centre, Caulfield hospital, and Pain services, Royal Melbourne hospital, or referred by GP/pain specialists. The treatment protocol had been published [1]. Participants were randomised into either REA, SEA, or PMM alone groups.

The treatment of REA was using disposable acupuncture needle (Hwato, Suzhou Medical Instrument Factory, Suzhou, China) of 0.25mm in diameter and 30 – 40mm in length to needle one side of Hegu (LI4), and Shousanli (LI10) as well as Zusanli (ST36) and Fenglong (ST40) on the same side. LI4 and LI10 were linked up with one pair of connecting wire with alligator clip adaptor (Figure 8.1) and ST36 and ST40 were linked up with another pair of connecting wire with alligator clip adaptor (Figure 8.2). These two pairs of needles were stimulated using E600 HAN Multi-purpose Digital Electronic Acupunctoscope (manufactured by Tens Plus Industrial Company, Hong Kong). The intensity of the REA stimulation was strong but comfortable with an alternating frequency of 2 and 100 Hz every three seconds and stimulation duration of 20 minutes. The four REA points alternated between left and right hand sides from treatment to treatment. Up to eight additional needles were used to address side effects of OM

totalling to a maximum of 12 needles used during each treatment (Table 8.1). These points were modified based on previous EA trial to reduce OM consumption [1079]. They included commonly used ST25, KI6, and SJ6 for constipation, CV4 and GV20 for fatigue. Deqi sensation, which was a numb, distending, or aching sensation, was achieved for all the points. Treatment frequency was two times per week from baseline week (commencement of randomisation) to week eight, once per week from week nine to week 10 (mid treatment week), and once every second week from week 11 to week 14 (end of treatment week). The total number of REA treatment sessions was 12.

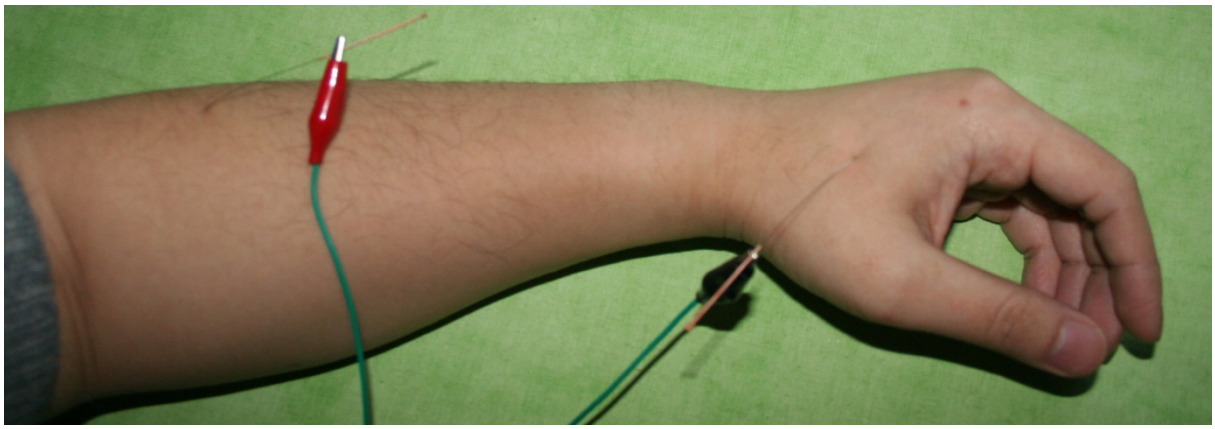


Figure 8.1 Needling LI4 and LI10 with connecting wire and alligator clip adaptor

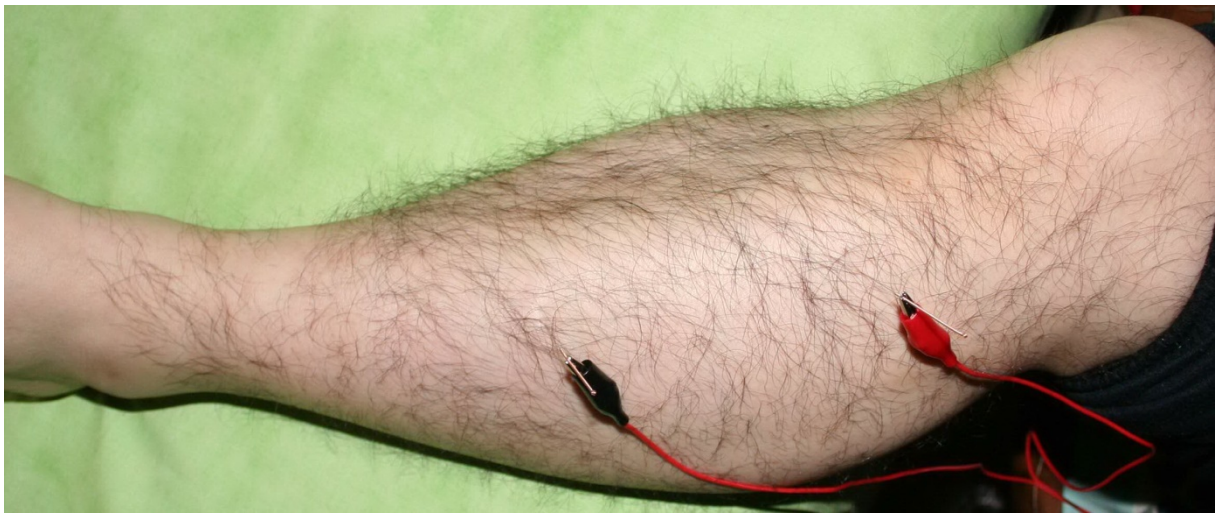


Figure 8.2 Needling ST36 and ST40 with connecting wire and alligator clip adaptor

Table 8.1 Additional acupuncture points for OM side effects

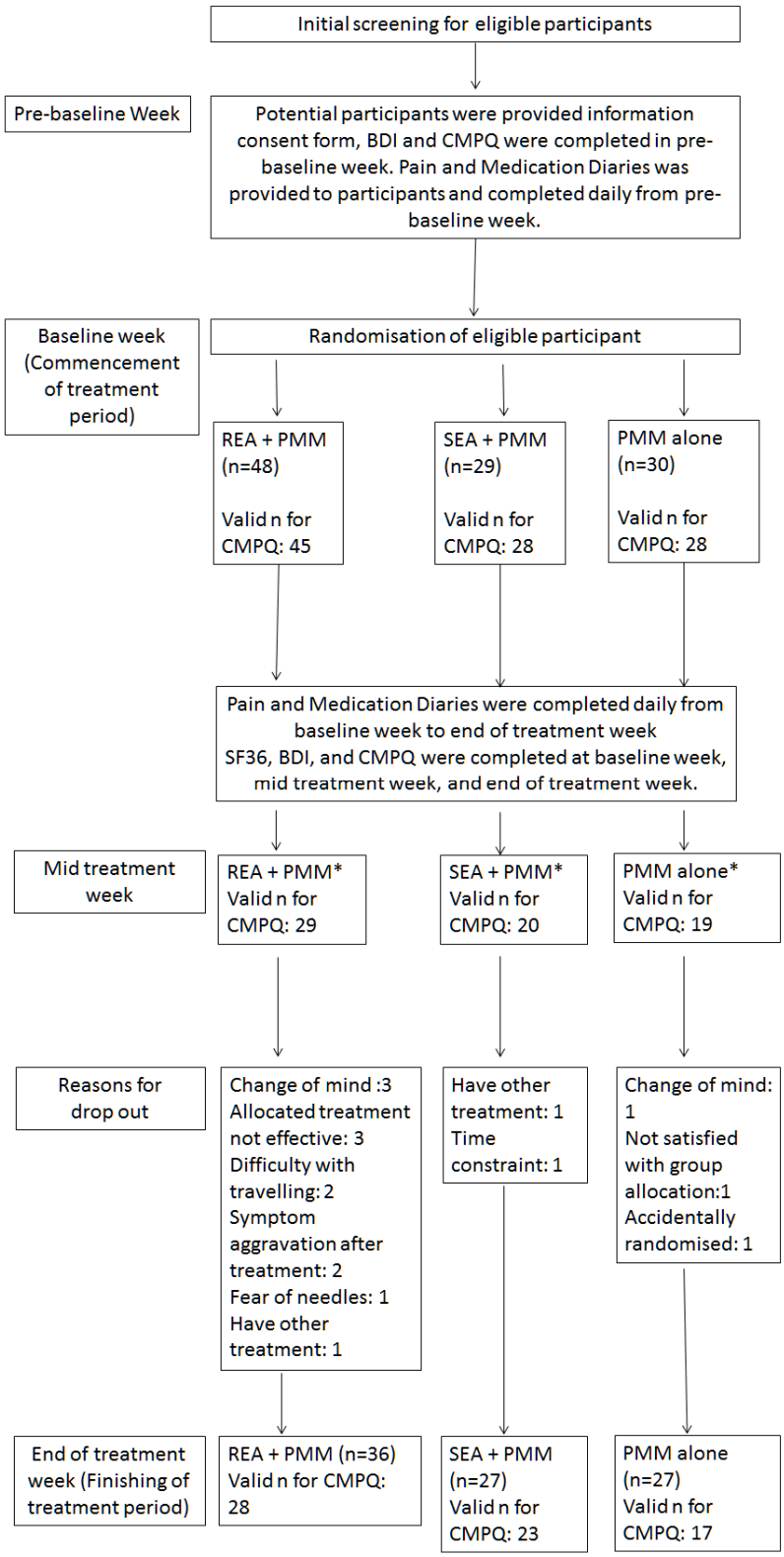
Adverse effects of OM	Acupuncture point selection	Recommended needle length	Depth of needling
Fatigue/General weakness/Lethargy	CV4, GV20	40mm 30mm	30-50mm 13-24mm
Constipation	ST25, KI6, SJ6	40mm	13 – 30mm
Drowsiness/sedation	SP9	40mm	30mm
Dizziness	GV20 LR3	30mm 30mm	13-24mm 13-24mm
Nausea	PC6	30mm	13-30mm
Night sweat	KI7, HT6	30-40mm	13-30mm
Insomnia	HT7, SP6	30-40mm	13-30mm
Nightmare	HT7, Yin Tang	40mm	13-30mm
Skin pruritus/skin itch	SP10	40mm	30mm
Dry mouth	LI3	30mm	20mm
Anxiety	Yin Tang, PC6	40mm	13-30mm
Blurred vision	GB38	40mm	30mm
Vomiting	BL17, PC6	30mm	20mm
Profuse sweating	KI7, LI4	40mm	13-30mm
Others	As appropriate	As appropriate	As appropriate

The same brand of needle was used for SEA. The needles were shallowly inserted onto points away from the REA points without manipulation or Deqi sensation. The locations of those sham points were standardised for the trial (Appendix 28). Each point used in REA all had a defined corresponding sham point. The sham LI4 and sham LI10 as well as sham ST36 and sham ST40 were connected to the non-functioning E600 HAN Multi-purpose Digital Electronic Acupunctoscope. The non-functioning machine had been modified by the manufacturer to emit light and sound, as the real machine did, without any current passing through the machine. This non-functioning machine had also been checked by the engineer of Alfred Health and Melbourne Health. Additional sham points were selected for side effect of OM (Appendix 28). These sham points were modified based on previous EA trial [1079]. The SEA treatment frequency and number of treatment was consistent with REA treatment.

All the three treatment groups received OM reduction schedule which aimed to help participants to reduce their use of OM to minimum. The proposed OM reduction was 30% by week eight, 50% by week 11, and 75% to 100% by week 14, which was the end of treatment week. If participants found the reduced OM dosage made their pain worse, participants were advised to go back to previous week's OM dosage and maintain at that level to the end of treatment week.

8.2.2 Outcome measures

The CMPQ that was developed in this project (Chapter 6 Initial development of CMPQ (p. 184)) was used to gather data for the symptoms of the participants. The items in the questionnaire included pain region, pain quality, pain rhythm, pain aggravator, pain alleviator, and other accompanying symptoms. The development of CMPQ had demonstrated content validity (Chapter 6.3.1 Content validity and face validity (p. 191)), internal consistency (Chapter 6.3.2 Internal consistency (p. 192)), and test-retest reliability (Chapter 6.3.3.1 Agreement (test-retest reliability) (p. 192)). Beck depression inventory, SF36, VAS for pain intensity, and OM consumption were also used as outcome measurements. Time point for completing these questionnaires and reasons of drop out were outlined in Figure 8.3.



BDI: Beck Depression Inventory
CMPQ: Chinese medicine pain questionnaire
REA: Real electro acupuncture
SEA: Sham electro acupuncture
EA: Electro acupuncture
PMM: Pain and medication management
SF36: Medical Outcome Short Form 36 Health Survey
*No data available for the sample size of each treatment group in mid treatment week.

Figure 8.3 Flow chart of completing questionnaires

8.2.3 Statistical analysis

Statistical Package for the Social Sciences version 22 was used for the statistical analysis. Frequency of each sign or symptoms was calculated for baseline and end of treatment weeks according to the treatment groups. Frequent symptoms were determined if their frequencies were more than 40%. To compare for baseline differences, one way ANOVA was used to assess the differences in total pain regions in baseline week amongst the three treatment groups. Two way ANOVA was used to assess the differences in the total pain region in baseline week sub grouped by the two CM patterns and the three treatment groups. Chi square analysis was used to assess if there was any statistically significant differences in the baseline week CMPQ items between the three treatment groups as well as when the CMPQ items were further sub grouped by the two CM patterns. Only participants who provided both baseline and end of treatment week's data were included for statistical analysis. Chinese medicine pain questionnaire items with $p<0.05$ in Chi square test was considered significantly different. MANOVA was also carried out to evaluate differences between the three treatment groups in baseline BDI, SF36, average pain intensity and average OM consumption.

Changes in signs and symptoms were based on changes between baseline and end of treatment weeks. The CMPQ items were all dichotomous (yes was represented by one and no was represented by zero). If a sign or symptom was present in any given week, the score "1" was given; if not present, the score "0" was given. Changes were calculated by subtracting the score of the previous week from the latter week (e.g. end of treatment week subtract baseline week). A value of zero meant no change, one meant new symptom arising and -1 meant symptom reduction. Table 8.2 provides three examples.

Table 8.2 Work out of change in symptoms between baseline and end of treatment weeks

Symptom	**Baseline week**	**End of treatment week**	**Changes between baseline and end of treatment weeks (overall treatment effect)**	**Interpretation**
Constipation	1	0	-1	Constipation alleviated
Fatigue	1	1	0	No change in fatigue in terms of its occurrence
Thirst	0	1	1	Thirst as a new symptom

To address aim number one, MANOVA was used to assess the association between the two

CM patterns and SF36, and BDI using baseline week data and average pain intensity and average OM consumption using the baseline weeks' data.

To address aim number two, Cochran's Q test was carried out to evaluate the significant changes ($p \leq 0.05$) in signs and symptoms amongst the individuals within the three treatment groups. The assumptions for the use of Cochran's Q test [1080] included 1) the response is dichotomous; 2) the subjects are independent of one another and randomly selected from a population; 3) the sample size is more than four and the number of subject (n) times the number of participants not showing the same results throughout the comparison (k) is more than 24 ($nk>24$). The results of Cochran's Q test were interpreted as either symptom improvement or symptom deterioration. If the overall changes were symptom reduction, this was symptom improvement. If the overall changes were symptom increased except for pain alleviator, this was symptom deterioration. Pain alleviator was interpreted the opposite way to the other domains e.g. overall changes were increased in alleviator meant symptom improving as participants found more alleviators to improve their pain. For Cochran's Q test, p value was maintained at 0.05 and not adjusted to 0.1 for significance level.

To address aim number three, Cochran's Q analysis was also carried out to evaluate which symptoms responded to the assigned treatment within CM heat pattern and CM cold with deficiency pattern (clusters four and five). Only the symptoms with $p<0.05$ in any of the treatment groups and CM patterns were presented in the results.

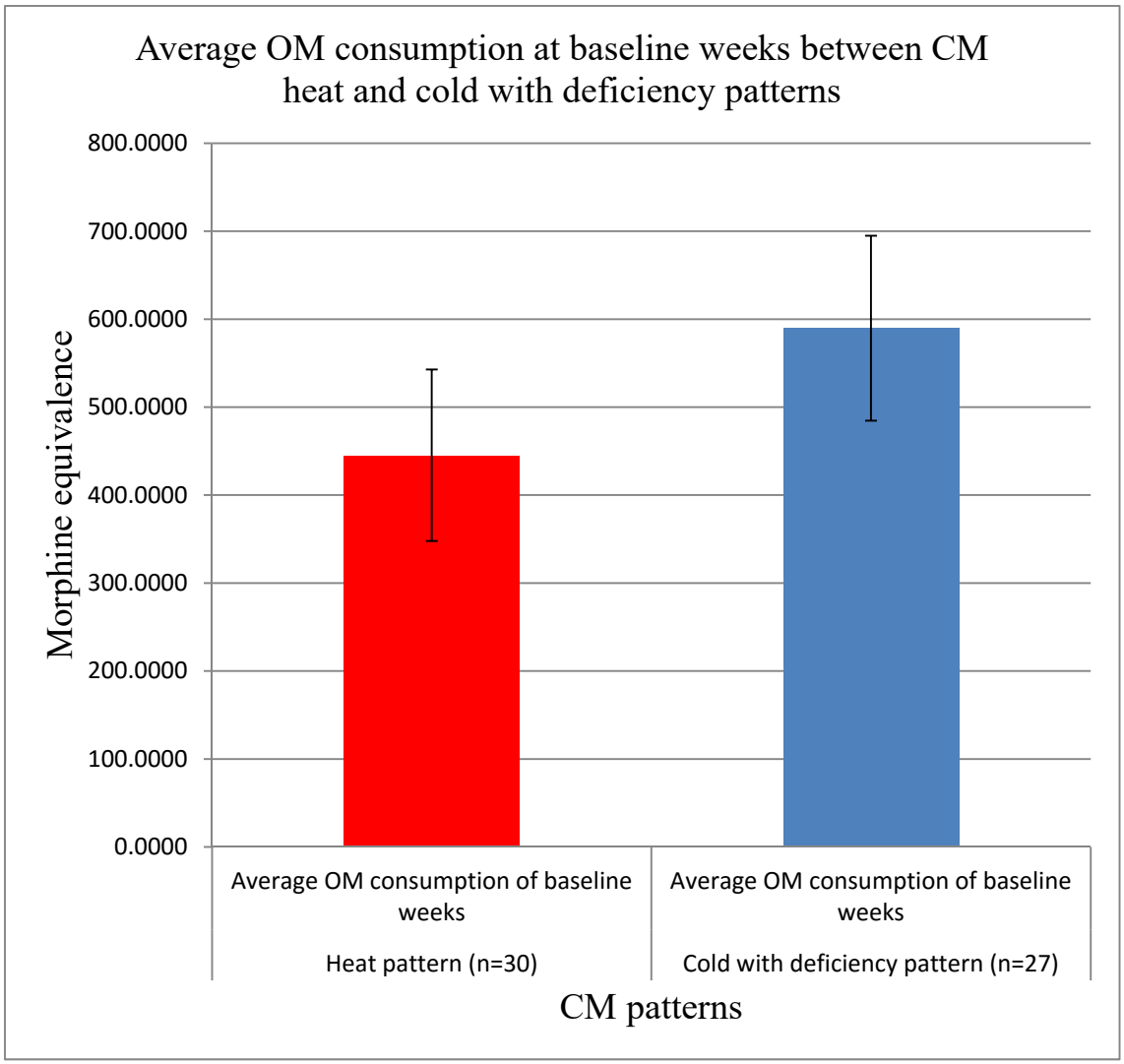
To address aim number four, baseline and end of treatment weeks data of BDI and SF36 as well as baseline weeks' and end of treatment weeks' data of average pain intensity and average OM consumption were used to assess which of the CM patterns reported best to the three treatments by using repeated MANOVA.

8.3 Result

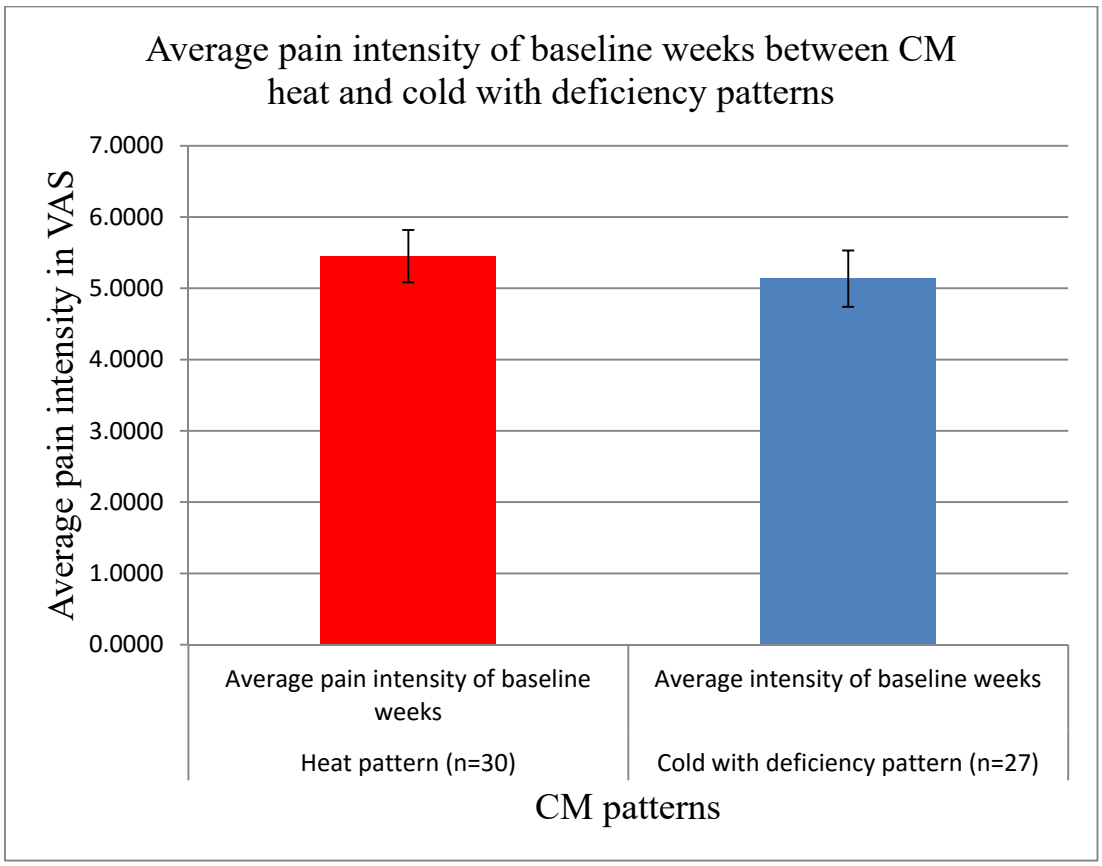
8.3.1 Differences of the two CM patterns

At the baselines, MANOVA showed that there were significant differences between the two CM patterns in baseline average of OM consumption, average of pain intensity, BDI, and SF36 total scores (Wilk's $\Lambda=0.814$, $F(4, 80) = 4.575$, $p=0.002$, partial $\eta 2=0.186$) (Appendix 29). Post-hoc one way ANOVAs were conducted for the four variables, with each evaluated at an α

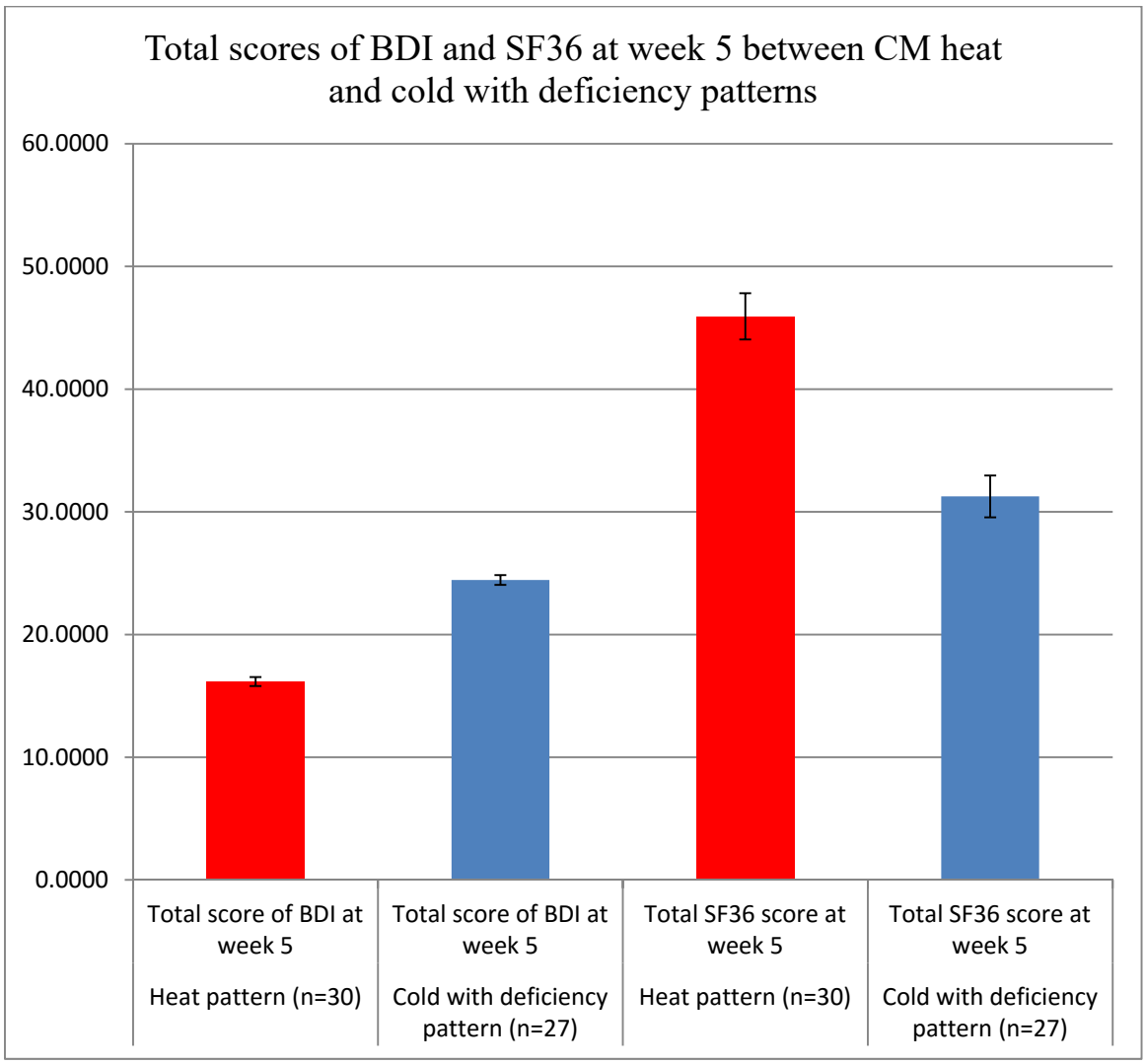
level of 0.0125. There were statistically significant differences between the two patterns on SF36 (F(1,83)=12.181, p=0.001, partial η2=0.128) (Figure 8.6) and on BDI (F(1,83)=9.068, p=0.003, partial η2=0.098) (Figure 8.6). Heat pattern (cluster four) (M=45.461) scored higher on SF36 than cold with deficiency pattern (cluster five) (M=32.016), reflecting better QoL (Appendix 29). Heat pattern (cluster four) (M=16.64) (mild depression) scored lower than cold with deficiency pattern (cluster five) (M=23.775) (moderate depression) on BDI, reflecting being less depressed. There are no differences between the two patterns in the average pain and OM consumption (Figure 8.4 and Figure 8.5).



Heat pattern: Mean: 445.2681. Standard error: 97.51359
Cold with deficiency pattern: Mean: 589.7261. Standard error: 105.1853
p=0.233
Figure 8.4 Average of OM consumption at baseline weeks of CM heat and "cold with deficiency" patterns



Heat pattern: Mean: 5.4511. Standard error: .36783
Cold with deficiency pattern: Mean: 5.1357. Standard error: 0.39459
p=0.152
Figure 8.5 Average pain intensity at baseline weeks of CM heat and "cold with deficiency" patterns



BDI:
Heat pattern: Mean: 16.1667. Standard error: 1.88526
Cold with deficiency pattern: Mean: 24.4444. Standard error: 1.70664
p=0.003
Total SF36:
Heat pattern: Mean: 45.9326. Standard error: 3.47133
Cold with deficiency pattern: Mean: 31.2577. Standard error: 3.53
p=0.001
Figure 8.6 BDI and SF36 scores at baseline week of CM heat and CM "cold with deficiency" patterns

8.3.2 CMPQ baseline comparison among three treatment groups

Baseline week comparison Table 8.3 to Table 8.5 list the significant differences in CMPQ symptoms of participants' baseline week data. Only those who had both baseline and end of treatment weeks data were included in the analysis. There were significant differences in the pain presentation amongst the three groups. Sham EA had more painful regions than REA and PMM alone (Table 8.3). And as shown in Table 8.4, when the three treatment groups were

further sub grouped into cluster 4 and cluster 5, the distribution of the symptoms differed more. Cluster four in SEA had more pain in wrist, front of the leg, and calf when compared with cluster five. Cluster five had more pain at fixed location than cluster four in REA and SEA. Cluster five's pain was more affected by physical movements than cluster four in the PMM alone group. Overall, cluster five had more symptoms than cluster four apart from pain region which showed the opposite. And when looking at the symptom distribution amongst the three treatment groups within clusters four and five, cluster four had the most uneven distribution of symptoms within the three treatment groups (Table 8.5).

Table 8.3 Significant difference for baseline week participants who also provide end of treatment week data and assessed by Chi square test (n=66)

Domains	**Symptom/factor**	**p value**	**Number of participants or mean and standard error (SE)**		
			REA (n=27)	**SEA (n=22)**	**PMM alone (n=17)**
Pain region	Shoulder	0.031	6	13	7
	Upper arm	0.035	6	12	4
	Elbow	0.016	2	9	3
	Forearm	0.01	2	8	1
	Wrist	0.016	3	10	3
	Fingers	0.044	4	9	2
	Front of the leg	0.008	2	10	4
	Total pain regions	0.008	6.56 (0.86)	11.0 (1.32)	7.0 (1.06)
Pain aggravator	Lying down	0.006	4	10	1
Other symptom	Thirsty	0.034	8	7	0

Table 8.4 Significant difference in CMPQ symptoms for baseline week participants sub grouped by the treatment groups and the two clusters assessed by Chi square test (n=57)

Domains	Symptom/ factor	Number of participants											
		REA (n=21)			SEA (n=21)			PMM alone (n=15)			Total (n=57)		
		p value[+]	Cluster 4 (n=13)	Cluster 5 (n=8)	p value[++]	Cluster 4 (n=11)	Cluster 5 (n=10)	p value[^]	Cluster 4 (n=6)	Cluster 5 (n=9)	p value[#]	Cluster 4 (n=30)	Cluster 5 (n=27)
Pain region	Frontal head	0.142	3	0	0.593	2	1	0.063	2	0	0.033*	7	1
	Side of the head	No value	0	0	0.314	3	1	0.018*	3	0	0.061	6	1
	Wrist	0.243	2	0	0.044*	7	2	0.292	2	1	0.025*	11	3
	Front of the leg	0.191	0	1	0.044*	7	2	0.057	0	4	0.82	7	7
	Calf	0.091	1	3	0.006*	6	0	0.475	1	3	0.697	8	6
Pain quality	Fixed location	0.011*	4	7	0.044*	4	8	0.519	3	3	0.024*	11	18
	Moving from one spot to another	0.091	1	3	0.223	1	3	0.057	0	4	0.005*	2	10
	Dull pain with weakness	0.854	2	1	0.049*	2	6	0.667	2	4	0.087	6	11
Pain rhythm	Worse during the day, better at night	0.716	1	1	0.007*	0	5	0.114	0	3	0.003*	1	9
	Worse at night, better during the day	0.854	2	1	0.031*	6	1	0.756	1	1	0.081	9	3
	Worse in the morning	0.058	0	2	0.05*	0	3	0.398	0	1	0.006*	0	6
	Worse in the afternoon	0.271	1	2	0.223	1	3	0.215	0	2	0.046*	2	7
Pain aggravator	Weather change	0.017*	0	3	0.097	1	4	0.114	0	3	0.001*	1	10
	Walking	0.027*	5	7	0.279	4	6	0.004*	2	9	0.001*	11	22
	Physical work	0.001*	3	8	0.256	5	7	0.004*	2	9	0*	10	24

Domains	Symptom/ factor	Number of participants											
		REA (n=21)			SEA (n=21)			PMM alone (n=15)			Total (n=57)		
		p value[+]	Cluster 4 (n=13)	Cluster 5 (n=8)	p value[++]	Cluster 4 (n=11)	Cluster 5 (n=10)	p value[^]	Cluster 4 (n=6)	Cluster 5 (n=9)	p value[#]	Cluster 4 (n=30)	Cluster 5 (n=27)
	Lifting	0.204	3	4	0.123	4	7	0.025*	2	8	0.002*	9	19
	Bending	0.006*	2	6	0.05*	3	7	0.02*	1	7	0*	6	20
	Going up/down stair	0*	1	7	0.835	5	5	0.025*	2	8	0*	8	20
	Driving	0.378	4	4	0.89	3	3	0.025*	0	5	0.091	7	12
	Bad night sleep	0.071	3	5	0.256	5	7	0.833	3	5	0.47	11	17
	Stress	0.378	4	4	0.072	6	9	0.085	2	7	0.01*	12	20
	Being emotional	0.477	3	3	0.13	3	6	0.057	1	6	0.013*	7	15
	Sex	0.716	1	1	0.223	1	3	0.057	0	4	0.023*	2	8
	Everything	0.005*	0	4	0.593	2	1	0.114	0	3	0.023*	2	8
	Household chores	0.006*	2	6	0.017*	2	7	0.132	1	5	0*	5	18
Pain alleviator	Hot packs	0.071	3	5	0.031*	5	9	0.398	2	5	0.005*	10	19
	Warm/hot shower	0.027*	1	4	0.835	5	5	0.095	3	1	0.574	9	10
	Lying down	0.965	5	3	0.269	2	4	0.025*	0	5	0.091	7	12
	Sitting	0.057	0	2	0.223	1	3	0.215	0	2	0.014*	1	7
	Resting	0.154	4	5	0.525	2	3	0.132	1	5	0.05*	7	13
	Deep breathing	0.017*	0	3	0.593	2	1	0.018*	3	0	0.848	5	4
	Bowel movement	0.191	0	1	no value	0	0	0.114	0	3	0.029*	0	4
	Pain killer	0.142	10	8	0.072	6	9	0.292	4	8	0.017*	20	25
Other symptoms	Heavy sensation in the body	0.854	2	1	0.696	3	2	0.018*	3	0	0.137	8	3
	Dry or sore	0.005*	0	4	0.89	3	3	0.756	1	1	0.132	4	8

Domains	Symptom/ factor	Number of participants											
		REA (n=21)			SEA (n=21)			PMM alone (n=15)			Total (n=57)		
		p value[+]	Cluster 4 (n=13)	Cluster 5 (n=8)	p value[++]	Cluster 4 (n=11)	Cluster 5 (n=10)	p value[^]	Cluster 4 (n=6)	Cluster 5 (n=9)	p value[#]	Cluster 4 (n=30)	Cluster 5 (n=27)
	throatp												
	Dry stool	No value	0	0	0.02*	0	4	0.398	0	1	0.014*	0	5
	Dry skin	0.027*	1	4	0.89	3	3	0.205	1	0	0.392	5	7
	Leak when sneezing or cough	0.017*	0	3	0.943	1	1	0.063	2	0	0.58	3	4
	Poor concentration	0.071	3	5	0.757	7	7	0.264	3	7	0.04*	13	19
	Low libido	0.02*	3	6	0.89	3	3	0.205	2	6	0.026*	8	15
	Poor appetite	0.477	3	3	0.864	4	4	0.025*	0	5	0.091	7	12
	Feeling tired easily	0.027*	5	7	0.407	7	8	0.519	3	6	0.03*	15	21
	Sigh often	0.058	0	2	0.525	2	3	0.264	1	4	0.031*	3	9
	Sweat upon mild activities	0.017*	0	3	0.916	2	2	0.833	3	4	0.144	5	9
	Feeling nervous easily	0.248	2	3	0.05*	3	7	0.132	1	5	0.005*	6	15
	Feeling depressed	0.006*	2	6	0.017*	2	7	0.085	2	7	0*	6	20
	Dizziness	0.271	1	2	0.049*	2	6	0.264	1	4	0.009*	4	12

* indicates statistical significance

For ease of reading, cell containing non-significant symptoms is shaded.

[+]the p value for clusters 4 and 5 comparison in REA

[++] the p value for clusters 4 and 5 comparison in SEA

[^] the p value for clusters 4 and 5 comparison in PMM alone

[#] the p value for clusters 4 and 5 comparison

Table 8.5 Significant difference in CMPQ symptoms for baseline week participants sub grouped by the two clusters and the treatment groups and assessed by Chi square test (n=57)

Domains	Symptom/factor	Number of participants or mean and standard error											
		Cluster 4 (n=30)				Cluster 5 (n=27)				Total (n=57)			
		p value+	REA (n=13)	SEA (n=11)	PMM alone (n=6)	p value++	REA (n=8)	SEA (n=10)	PMM alone (n=9)	p value^	REA (n=21)	SEA (n=21)	PMM alone (n=15)
Pain region	Side of the head	0.03*	0	3	3	0.414	0	1	0	0.097	0	4	3
	Back of the head	0.028*	1	5	0	0.414	0	1	0	0.015*	1	6	0
	Neck	0.011*	2	8	4	0.187	1	5	2	0.007*	3	13	6
	Shoulder	0.004*	1	8	3	0.53	2	5	3	0.007*	3	13	6
	Upper arm	0.015*	1	7	2	0.368	2	5	2	0.011*	3	12	4
	Elbow	0.211	1	4	1	0.074	0	4	1	0.019*	1	8	2
	Forearm	0.006*	0	5	0	0.842	1	2	1	0.021*	1	7	1
	Wrist	0.05*	2	7	2	0.407	0	2	1	0.038*	2	9	3
	Fingers	0.002*	0	7	1	0.754	2	2	1	0.022*	2	9	2
	Thigh	0.049*	3	6	0	0.914	4	4	4	0.401	7	10	4
	front of the leg	0*	0	7	0	0.281	1	2	4	0.016*	1	9	4
	Calf	0.029*	1	6	1	0.101	3	0	3	0.755	4	6	4
	Chest	0.028*	1	5	0	0.379	1	2	0	0.016*	2	7	0
	Total pain region	0.003*	4.69 (1.17)	12.72 (5.93)	8.17 (6.18)	0.534	6.5 (4.11)	8.5 (6.00)	6.22 (3.60)	0.004*	5.38 (4.18)	10.71 (6.21)	7.00 (4.42)
Pain quality	Fixed location	0.721	4	4	3	0.032*	7	8	3	0.589	11	12	6
Pain aggravator	Lying down	0.028*	1	5	0	0.327	3	4	1	0.035*	4	9	1
Pain alleviator	Deep breathing	0.024*	0	2	3	0.082	3	1	0	0.873	3	3	3
Other symptoms	Cold hands and feet	0.438	2	4	1	0.024*	1	5	0	0.019*	3	9	1
	Irritable	0.511	3	5	2	0.027*	1	5	7	0.033*	4	10	9
	Thirsty	0.349	2	3	0	0.094	3	4	0	0.05*	5	7	0
	Poor memory	0.105	2	6	3	0.074	3	5	8	0.011*	5	11	11

	Sweat upon mild activities	0.024*	0	2	3	0.506	3	2	4	0.064	3	4	7

* indicates statistical significance

For ease of reading, cell containing non-significant symptoms is shaded.

[+]the p value for clusters 4 distribution in the three treatment groups

[++] the p value for clusters 5 distribution in the three treatment groups

[^] the p value for participant distribution in the three treatment groups for only clusters 4 and 5

Based on the Chi square tests (Table 8.3), the three treatment groups differed significantly in some of the symptoms in baseline week and the three treatment groups' distribution over the two clusters (Table 8.4) as well as the two cluster distribution over the three treatment groups (Table 8.5) differed significantly in various symptoms. And due to the number of dropouts (n=35 or 33%), changes in percentages between baseline and end of treatment weeks were not analysed.

Average OM consumption, average pain intensity, BDI and SF36 were compared amongst REA, SEA, and PMM alone groups using MANOVA. There was no difference between the three treatment groups (Wilk's Λ=0.866, F(8, 120)=1.122, p=0.353, partial $\eta 2$=0.070). Separate ANOVA showed there were no difference between groups in average OM consumption (p=0.42), average pain intensity (p=0.183), BDI (p=0.27), and SF36 (p=0.388) (Table 8.6). Comparison of these pain data and BDI, and SF36 between cluster four and five are presented in this chapter section 8.3 (p. 266).

Table 8.6 Comparison of average OM dosage and pain over baseline weeks, and BDI and SF36 data at baseline week (MANOVA)

Treatment group									
					95% Confidence Interval		ANOVA		
Dependent Variable	Treatment group	n	Mean	Std. Error	Lower Bound	Upper Bound	F	df	Sig.
Average of OM consumption at baseline weeks	REA	27	482.712	125.195	232.530	732.894	0.880	2	0.420
	SEA	22	672.862	138.694	395.705	950.020			
	PMM alone	17	412.182	157.777	96.889	727.475			
Average pain intensity at baseline weeks	REA	27	4.741	0.388	3.965	5.516	1.743	2	0.183
	SEA	22	5.815	0.430	4.956	6.675			
	PMM alone	17	5.342	0.489	4.364	6.320			
Total score of BDI at baseline week	REA	27	17.444	2.090	13.268	21.621	1.336	2	0.270
	SEA	22	20.818	2.315	16.192	25.445			
	PMM alone	17	22.706	2.634	17.443	27.969			
Total SF36 score at baseline week	REA	27	41.538	3.706	34.132	48.943	0.961	2	0.388
	SEA	22	38.781	4.105	30.577	46.985			
	PMM alone	17	33.287	4.670	23.954	42.620			

Percentage of CMPQ symptoms of baseline and end of treatment weeks are summarised in Appendix 30. The raw frequency tables of baseline and end of treatment weeks are listed from Appendix 31 to Appendix 60. Due to the small number of female subjects (n=15 for females under 51 years old), CM items related to gynaecological problem were not analysed.

8.3.3 Changes in signs and symptoms between baseline week and end of treatment week

For this section (Chapter 8.3.3) and the next section (Chapter 8.3.4) only symptoms with significant changes are presented. Symptoms not presented meant no significant changes (e.g. p>0.05).

For the three assumptions of Cochran's Q test described in Chapter 8.2.3 Statistical analysis (p. 265). Criteria one and three were met. Chinese medicine pain questionnaire was designed with dichotomous outcome, and the n times k was greater than 24. N was at least six (CM heat pattern in PMM alone group) and k was 163 (Table 5.6p. 160). The only assumption that was partly met was the recruitment of the subjects were a convenient sample from the pain clinic or referred by specialists/GP rather than a randomly selected sample and participants were independent of one another.

For REA (n=27), there were only two significant improvements between baseline and end of treatment weeks (Table 8.7). There were four fewer participants having nausea and five fewer participants feeling "nothing" alleviates their pain. Feeling nothing alleviated their pain indicated participants did not feel there was any pain alleviator, reflecting five more participants found their pain becoming responsive to interventions or strategies.

Table 8.7 Significant changes between baseline and end of treatment weeks in REA group (n=27)

Domain	Sub-categories	Item	Overall changes*	p-values
Pain alleviator	Other	nothing	-5	0.025
Other symptoms	&	nausea△	-4	0.046

* Positive value means more participants experience such symptom/description and vice versa. Positive value indicates symptom worsening except for pain alleviator which is the opposite. And negative value in "nothing" as alleviator indicates improvement.
△ Indicates related to OM side effects
& no sub category for other symptoms

For SEA (n=22), there was a mixture of improvement and deterioration between weeks five and 14 (Table 8.8). The improvements included four to five more participants having pain reduction in upper limb, or sacrum area. Seven fewer participants had pain in fixed location, four to six more participants found reading and "keeping their mind off pain" alleviated their pain. There were five to seven fewer participants suffering from nausea, dizziness, and poor appetite. Deterioration on the other hand included there were four more participants

experienced pain on the side of the body and seven more participants experienced pain aggravated by cold weather.

Table 8.8 Significant changes between baseline and end of treatment weeks in SEA group (n=22)

Domain	Sub-categories	Item	Overall changes*	p-values
Pain regions	Upper limb	upper arm	-5	0.025
		forearm	-4	0.046
	Front of the body	side of the body	4	0.046
	Back of the body	sacrum	-4	0.046
Pain quality	&	fixed location	-7	0.02
Pain aggravator	Environmental changes	cold weather	7	0.008
Pain alleviator	Physiological and psychic changes	reading	4	0.046
		keeping my mind off pain	6	0.034
Other symptoms	&	nausea△	-7	0.008
		dizziness	-6	0.014
		poor appetite	-5	0.025

* Positive value means more participants experiences such symptom/description and vice versa. Positive value indicates symptom worsening except for pain alleviator which is the opposite.△ Indicates related to OM side effects
& no sub category for pain quality and other symptoms

For PMM alone (n=17), the changes between baseline and end of treatment weeks were also a mixture of improvements and deteriorations (Table 8.9). Improvements included four fewer participants felt their pain were numb, aggravated by “any movement”, suffered from poor memory and four more participants felt warm/hot shower alleviated their pain. On the other hand, the deterioration included four to five more participants had pain between shoulder blade or felt cold weather aggravated their pain.

Table 8.9 Significant changes between baseline and end of treatment weeks in PMM alone group (n=17)

Domain	Sub-categories	Item	Overall changes*	p-values
Pain regions	Back of the body	between shoulder blades	4	0.046
Pain quality	&	numbness	-4	0.046
Pain aggravator	Environmental changes	cold weather	5	0.025
	Exercises or sporting	any movement	-4	0.046
Pain alleviator	Environmental changes	warm/hot shower	4	0.046
Other symptoms	&	poor memory	-4	0.046

* Positive value means more participants experiences such symptom/description and vice versa.

Positive value indicates symptom worsening except for pain alleviator which is the opposite.
& no sub category for pain quality and other symptoms

8.3.4 Changes in signs and symptoms according to treatment groups and clusters between baseline and end of treatment weeks

The cluster distribution amongst different treatment group is listed in Table 8.10. Only participants who presented data for both baseline and end of treatment weeks were included. Most of the participants were from clusters four and five.

Table 8.10 Distribution of clusters in the three treatment groups which provided both baseline and end of treatment weeks data

Cluster	REA	SEA	PMM alone
1	0	0	0
2	2 (7.4%)	0	1 (5.9%)
3	0	1 (4.5%)	0
4	13 (48.1%)	11 (50%)	6 (35.3%)
5	8 (29.6%)	10 (45.5%)	9 (52.9%)
6	4 (14.8%)	0	1 (5.9%)

Percentage shown is the proportion of cluster in each treatment group

REA (n=27)

For REA group, in comparison of clusters four and five, cluster four reported four fewer participants experienced worse pain when first getting up and four more participants found hot packs alleviated their pain (Table 8.11). Cluster five on the other hand reported four fewer participants had pain at a fixed location.

Table 8.11 Significant changes between baseline and end of treatment weeks in REA group with cluster information (n=21)

Domain	Sub-categories	Item	Cluster 4 (n=13)		Cluster 5 (n=8)	
			Overall changes*	p-values	Overall changes*	p-values
Pain quality	&	Fixed location	1	0.655	-4	**0.046**
Pain rhythm	&	Worse when first get up	-4	**0.046**	−2	0.317
Pain	Environmental	Hot packs	4	**0.046**	−1	0.564

Domain	Sub-categories	Item	Cluster 4 (n=13)		Cluster 5 (n=8)	
			Overall changes*	p-values	Overall changes*	p-values
alleviator	changes					

* Positive value means more participants experiences such symptom/description and vice versa. Positive value indicates symptom worsening except for pain alleviator which is the opposite.
Bold font indicates significant difference at $p<0.05$
& no sub category for pain quality and other symptoms

SEA (n=22)

In comparison of both clusters four and five, cluster four reported as four more participants experienced reductions in painful regions, four fewer participants experienced pain all the time, and four to five fewer participants experienced the digestive symptoms (poor appetite and nausea) (Table 8.12). Cluster five on the other hand showed improvements in six fewer participants feel pain at a fixed location, four more participants felt by "keeping busy" alleviated their pain, and four fewer participants had swollen joints, dizziness, and dry stools. In addition, cluster five also showed four more participants experienced pain aggravated by "cold weather" (Table 8.12).

Table 8.12 Significant changes between baseline and end of treatment weeks in SEA group with cluster information (n=22)

Domain	Sub-categories	Item	Cluster 4 (n=11)		Cluster 5 (n=10)	
			Overall changes*	p-values	Overall changes*	p-values
Pain regions	Lower limb	Calf	-4	**0.046**	2	0.157
		Front of the leg	-4	**0.046**	-1	0.317
Pain quality	&	Fixed location	-1	0.564	-6	**0.014**
Pain rhythm	&	All the time	-4	**0.046**	0	1
Pain aggravator	Environmental changes	Cold weather	3	0.083	4	**0.046**
Pain alleviator	Other	Keeping busy	0	1	4	**0.046**
Other symptoms	&	Poor appetite	-4	**0.046**	-1	0.317
		Nausea△	-5	**0.025**	-2	0.157
		Swollen joints	-1	0.655	-4	**0.046**
		Dizziness	-2	0.157	-4	**0.046**
		Dry stools△	1	0.317	-4	**0.046**

* Positive value means more participants experiences such symptom/description and vice versa.

Positive value indicates symptom worsening except for pain alleviator which is the opposite.
Bold font indicates significant difference at $p<0.05$
△ Indicates symptom related to OM side effects
& no sub category for pain quality and other symptoms

PMM alone (n=17)

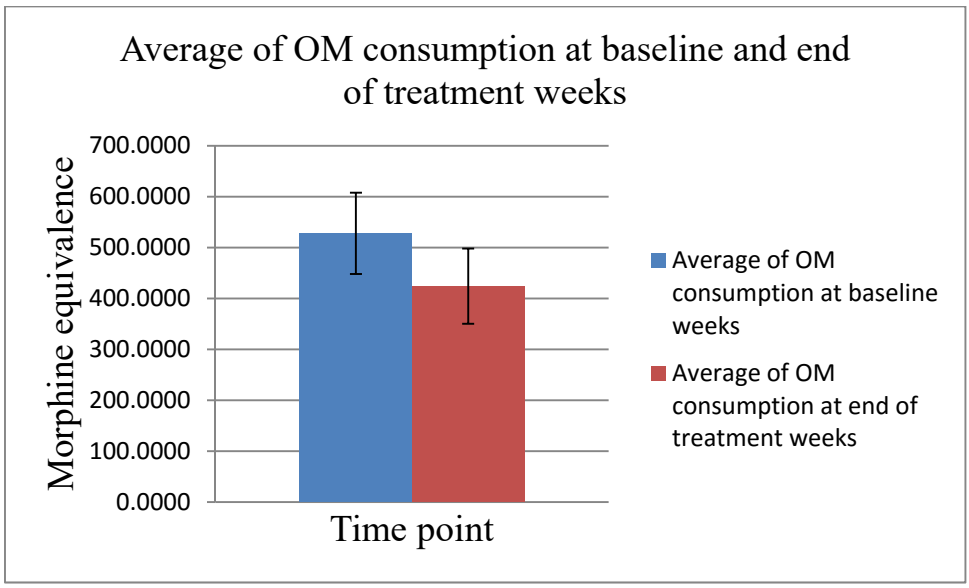
Only cluster five showed significant changes between baseline and end of treatment weeks in PMM alone group (Table 8.13). The only change was four fewer participants felt their pain as numbness.

Table 8.13 Significant changes between baseline and end of treatment weeks in PMM alone group with cluster information (n=15)

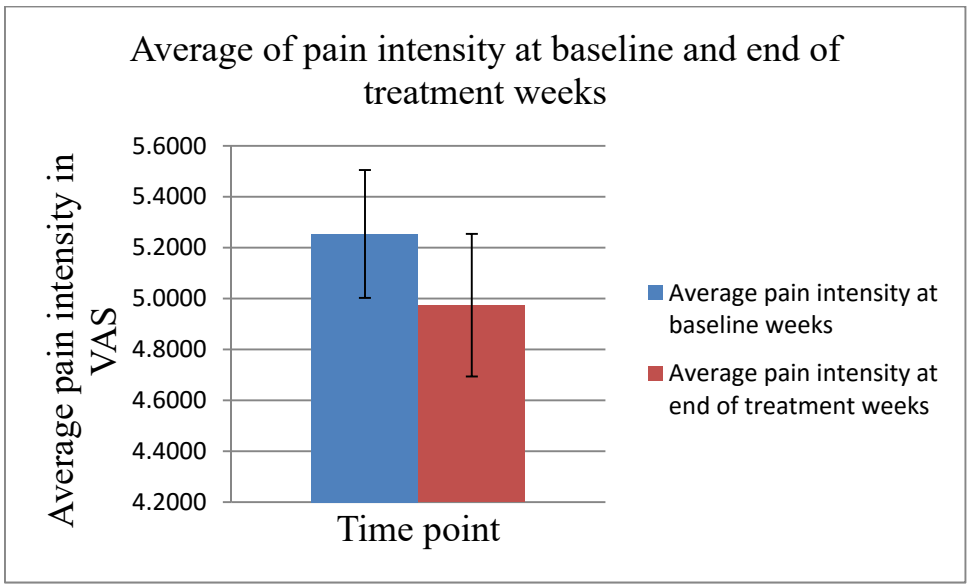
Domain	Item	Cluster 4 (n=6)		Cluster 5 (n=9)	
		Overall changes*	**p-values**	**Overall changes***	**p-values**
Pain quality	Numbness	0	1	-4	**0.046**

* Positive value means more participants experiences such symptom/description and vice versa.
Positive value indicates symptom worsening except for pain alleviator which is the opposite.
Bold font indicates significant difference at $p<0.05$

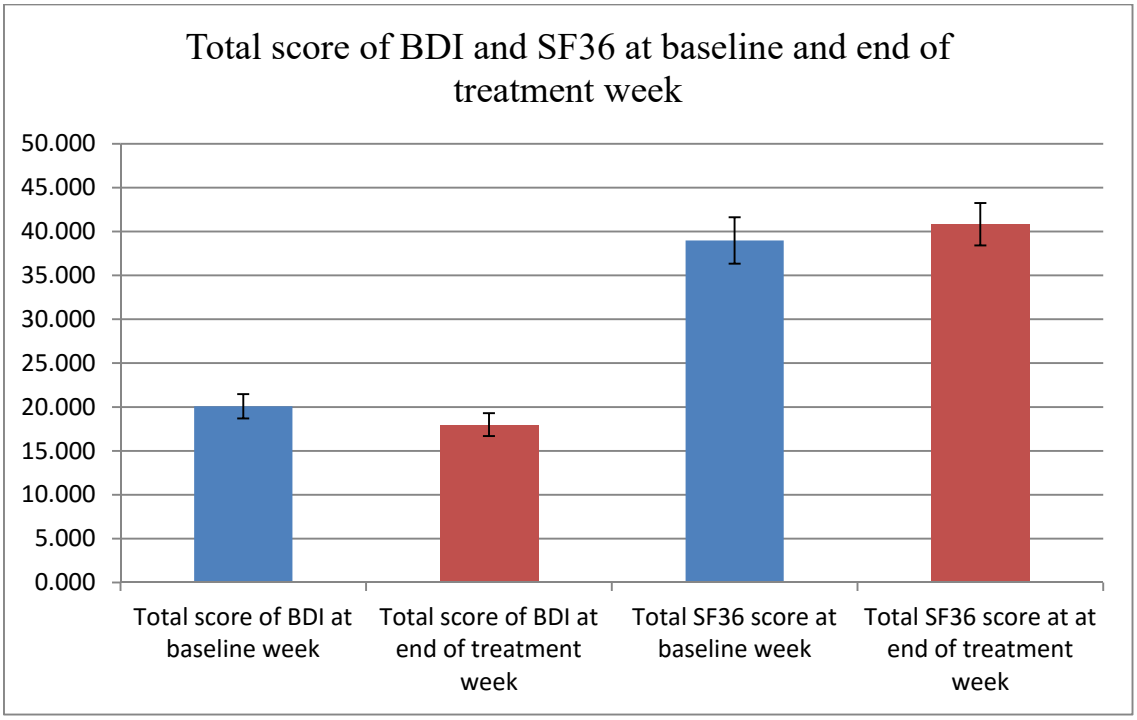
Repeated MANOVA was used to assess the effects of the three treatments, and the treatment effects on the two CM patterns in the four outcome measures (average pain intensity, average OM consumption, total SF36 score, and BDI). Over time, only average OM consumption (Figure 8.7) and BDI (Figure 8.9) showed statistically significant improvements and not total SF36 score (Figure 8.9) and average pain intensity (Figure 8.8) (Table 8.14). Over time, there were no statistical significant changes in the two CM patterns after the three treatments in the four assessments (Table 8.14, Appendix 61 to Appendix 72).



Baseline weeks: Mean: 513.696. Standard error: 71.539
End of treatment weeks: Mean: 414.580. Standard error: 67.545
p=0.000*
Figure 8.7 Average OM consumption amongst all participants between baseline and end of treatment weeks (n=57)



Baseline weeks: Mean: 5.302. Standard error: 0.268
End of treatment weeks: Mean: 5.029. Standard error: 0.298
p=0.122
Figure 8.8 Average pain intensity amongst all participants between baseline and end of treatment weeks (n=57)



Total score of BDI:
Baseline week: Mean: 20.088. Standard error: 1.384
End of treatment week: Mean: 18.000. Standard error: 1.302
p=0.014*

Total SF36 score:
Baseline week: Mean: 38.981. Standard error: 2.643
End of treatment week: Mean: 40.830. Standard error: 2.424
p=0.296
Figure 8.9 BDI, and SF36 scores of all participants between baseline and end of treatment weeks (n=57)

Table 8.14 Repeated MANOVA for SF36, average OM, average pain, and BDI, and treatment group, and time (n=66)

Outcome measure	n	Wilk's Λ	F	Hypothesis df	Error df	p value	partial $\eta 2$
Repeated MANOVA over time							
SF36	57	0.978	1.171[b]	1.000	51.000	0.284	0.022
Average OM consumption	57	0.722	19.611[b]	1.000	51.000	0.000	0.278
Average pain intensity	57	0.959	2.204[b]	1.000	51.000	0.144	0.041
BDI	57	0.875	7.315[b]	1.000	51.000	0.009	0.125
Repeated MANOVA over time and CM patterns							
SF36	57	0.966	1.780[b]	1.000	51.000	0.188	0.034
Average OM consumption	57	0.988	0.598[b]	1.000	51.000	0.443	0.012
Average pain intensity	57	0.982	0.922[b]	1.000	51.000	0.342	0.018
BDI	57	0.966	1.772[b]	1.000	51.000	0.189	0.034
Repeated MANOVA over time and treatment group							
SF36	57	0.937	1.701[b]	2.000	51.000	0.193	0.063
Average OM consumption	57	0.925	2.060[b]	2.000	51.000	0.138	0.075
Average pain intensity	57	0.992	0.200[b]	2.000	51.000	0.819	0.008
BDI	57	0.998	0.054[b]	2.000	51.000	0.948	0.002
Repeated MANOVA over time, treatment group, and CM patterns							
SF36	57	0.948	1.407[b]	2.000	51.000	0.254	0.052
Average OM consumption	57	0.940	1.632[b]	2.000	51.000	0.206	0.060
Average pain intensity	57	0.986	0.358[b]	2.000	51.000	0.701	0.014
BDI	57	0.915	2.356[b]	2.000	51.000	0.105	0.085

* Indicate statistical significance (P<0.05)
b. Exact statistic
SF36: Medical outcome short form health survey 36 items
BDI: Beck Depression Inventory
CM: Chinese medicine
OM: Opioid medication

8.4 Discussion

8.4.1 Summary of findings

This chapter aimed to 1) identify the group difference between the CM "heat" and "cold with deficiency" patterns; 2) identify if CMPQ could assess changes after treatment and if different treatments induced different changes; 3) identify which pattern responded best to REA treatment; 4) find out if the CM "heat" and "cold with deficiency" patterns differed in treatment response in the four outcome measures (average pain intensity, average OM consumption, SF36 and BDI) between baseline weeks and the end of treatment weeks.

For aim number one, CM heat pattern (cluster four) was associated with a better QoL and mild depression over CM cold with deficiency pattern (cluster five) at baseline week.

For aim number two CMPQ could capture changes in signs and symptoms after treatments. Real EA group participants reported improvement in nausea symptom and perception of treatment where less of them felt nothing improves their pain; SEA group participants reported improvement in painful regions, pain at fixed location, participant's response to reading and keeping their mind off pain, and nausea, dizziness, and poor appetite symptoms, and at the same time SEA group reported more pain aggravation to cold weather; and PMM alone group participants reported improvement in the numbness sensation, pain aggravated by movement, response to warm/hot shower, and poor memory, at the same time they also reported deteriorated response in more pain in between the shoulder blade, and more pain aggravation by cold weather.

For aim number three, there were differences in how the two patterns responded to REA treatment based on CMPQ items. Chinese medicine heat pattern (cluster four) reported better results to REA in comparison to CM cold with deficiency pattern (cluster five) where CM heat pattern had more pain alleviation to hot packs. Chinese medicine heat pattern reported slightly better to REA in having one more symptom improved than CM cold with deficiency pattern. Neither of the two patterns reported best response to REA treatment.

For aim number four, there was no significant difference in treatment responses of the two CM patterns over time for average pain intensity and average OM consumption, QoL, and depression.

Chinese medicine pain questionnaire was developed and designed to standardise and assist CM consultation. Evaluating the presence/absence of symptoms after treatment is a common practice in CM. According to Chinese Medicine Board of Australia, the requirement of the patient case record includes noting down the relevant changes of the ongoing conditions during the subsequent consultation [1081]. The results of this project indicated CMPQ captured minor changes in symptoms (Table 8.15).

8.4.2 Association of CM clusters with other outcome measures

Chinese medicine heat pattern (cluster four) was associated with better QoL and depression in comparison to CM cold with deficiency pattern (cluster five) despite the two patterns had similar pain intensity and OM usage. Other similar studies related to the association between pain and other outcome measures included TMD and perceived physical symptoms, psychological, coping and psychosocial variables [1082]. Suvinen et al. found the 41 female TMD participants could be classified into simple (22%), intermediate (41%), and complex (37%) clusters [1082]. The three clusters did not differ significantly in the pain intensity, which was similar to the current study. The simple cluster contained patient who had mainly physical symptom and low scores on psychological and psychosocial variables. The psychological variables included the Coping Strategies Questionnaire, Illness Behaviour Questionnaire, BDI, and Beck Anxiety Inventory. The psychosocial variables were part one of Multidimension Pain Inventory. The complex cluster had considerable psychological and psychosocial dysfunction irrespective of the severity of the physical symptoms. The intermediate cluster had abilities to manage and cope with their conditions irrespective of the physical or psychosocial dysfunctions.

The current study differed from them in the participants recruited were CMP and the interpretation of cluster was in CM way. Other similar study who also used CM understanding to interpret the meaning of clusters included Hao [1083] who developed a CM headache questionnaire, used factor and cluster analysis to group symptoms of tension type headache, and compared participants' disability using Migraine Disability Assessment Questionnaire (MIDAS) [1084] and psychological stress using Perceived Stress Scale scores [1085]. MIDAS evaluates the disability using the number of days patients suffering from reduced productivity due to headache, number of days having headache, and severity of headache. Hao's study had identified four clusters. In CM interpretation, cluster one was ascendant hyperactivity of CM liver Yang, cluster two was dual deficiency of Qi and blood, and cluster three was CM liver

depression forming fire, and cluster four was a nonspecific cluster. Of these four clusters, although the overall MIDAS score, and the number of headache days did not differ in the four clusters, cluster one was of moderate headache intensity and disability, and performed the best in perceived coping ability of stress among the four clusters. Cluster two on the other hand had the worst headache and highest disability. Cluster three had moderate headache intensity and severe disability. Cluster four had the mildest headache intensity, moderate disability and was free from mental comorbidity. Of the four cluster's perceived stress, cluster one and two seemed to cope stress better than cluster three and four as stated by Hao [1083]. The findings of this project and Hao's study highlight that apart from the pain severity, medication usage, disability, depression, and QoL, CM pattern identification can further sub group chronic pain patient and these subgroups may or may not differ in standard assessments.

The association between CM pattern and QoL have been explored in other studies [1086,1087]. Luo et al. finds diabetic patients with Qi deficiency pattern had lower QoL in every aspects of WHO Quality of Life (WHOQOL-BREF) and SF12 [1086] when compared with participants without Qi deficiency pattern. Song et al. finds obese women with CM liver depression and Qi stagnation pattern had the lowest mental component summary (MCS-12) score in comparison to the control group but not in physical component summary (PCS-12) and WHOQOL-BREF [1087]. The control group comprised of obese patients who could not be classified into any of the predefined five CM patterns, including "CM spleen deficiency with dampness obstruction", "CM stomach heat with dampness obstruction", "CM liver depression and Qi stagnation", "both CM spleen and CM kidney deficiencies", and "Yin deficiency with internal heat". The results of the current study was similar to Luo et al.'s study where participants with deficiency pattern scores the worst [1086] but different from Song et al.'s result where CM liver depression and Qi stagnation pattern scores the worst QoL emotionally but not physically [1087]. Such difference may be due to the participants recruited and the QoL assessment utilised, and the use of OM for pain control indicated the participants' CMP was more advanced [1073]. Song et al. pre-defined CM patterns based on literature review [1087] and the current project utilised scientific sound cluster analysis to group the symptom presentation.

8.4.3 Consideration of statistical analysis and sample size

The project utilised Cochran's Q test to analyse changes in the dichotomous CMPQ items. Assumptions one and three of Cochran's Q pre-requisites were met but assumption two was only partially met where the participant recruitment was from a convenience sample and not

randomly selected from the population. The inclusion criteria of the recruited participants included the use of OM for more than three months. Opioid medication is a controlled schedule eight substance and requires the permit from the government for long term use [1088]. Such requirement made random sampling impossible. Other studies have also used convenience sample and used Cochran's Q analysis to analyse the outcome [1089,1090].

Choosing only the participants who provided both baseline and end of treatment weeks made the sample size smaller. It was necessary to use this approach as no last value carried forward was used for CMPQ. It was not suitable to take the data of participants who dropped out of the study to compare their other outcome measure using last value carried forward due to no CMPQ data at later stage. It was necessary to remove these participants and statistically it is acceptable to remove data that were missing complete at random, also known as complete case analysis [1091].

The sample size became smaller when sub grouped by the treatment groups and the CM patterns. This impacts on the results. It was observed Cochran's Q test requires at least four participants to show improvements/deteriorations in one symptom to achieve $p<0.05$. The greyed items in Table 8.15 indicate the groups with less than four participants presenting with such symptom in baseline week. This small sample size made it difficult to detect changes in these items. And with the baseline differences, as shown in Table 8.3, Table 8.4, and Table 8.5 (p. 270 to 274), this limited the comparability amongst the groups. However, a small sample size can have large p value for statistically significant difference [1092(p576)], not to mention the $p<0.05$ achieved in the Cochran's Q analysis, and Cochran's Q analysis is comparing within individual changes and not group changes. This further enhanced the validity of the results.

8.4.4 Interpretation of findings - number of pain regions

The ANOVA results showed significant differences amongst the three treatment groups at baseline week when totalling the pain regions for the three treatment groups amongst participants who also provided data for both baseline and end of treatment weeks (REA M=6.56, SEA M=11.00; PMM alone: M=7.00). Overall, SEA group had the greatest improvement in pain regions amongst the three treatment groups. This difference in change perhaps reflects a baseline difference.

8.4.5 Interpretation of findings – sensitivity to temperature

Amongst all the symptoms that showed statistically significant differences, REA was the group with no deteriorations whereas SEA and PMM alone both have two symptom deteriorations. Importantly only REA showed no further pain aggravation by cold weather, whereas SEA and PMM alone both had their pain further aggravated by cold weather (Table 8.15). Such finding consistently occurred in both CM heat and CM "cold with deficiency" patterns in SEA and cold with deficiency pattern in PMM alone (Table 8.16). Due to there were less than four participants to improve, such finding did not show in CM heat pattern in PMM alone (Table 8.16).

Comparatively, CM heat pattern had enough participants for improvement in pain alleviated by "hot packs" in all three treatment groups. Only REA group showed improvement (Table 8.16). Chinese medicine "cold with deficiency" pattern either had insufficient participants for improvement in REA and SEA groups or was showing no significant difference in PMM alone group (Table 8.16).

Hay et al. compared painful stimulation by von Frey hairs, electrical stimulation, and cold pressor on noncancer chronic pain patients taking OM in comparison to those not taking OM found the tolerance time to cold pressor of patients on OM (18.1-19.7 ± 1.9-2.6 seconds) was shorter than the OM naive patients (30.7 ± 3.9 seconds) [1093]. Zahari et al. had also found similar findings in OM dependent patients and OM naive patients, the cold pressor tolerance time of the two groups was 34.17 seconds (95% CI 24.86, 43.49) and 61.36 seconds (52.23, 70.48) ($p<0.001$), respectively. Both studies showed cold intolerance in patients taking OM.

The current study adds two newer information to this finding in 1) REA group although were still on OM, their sensitivity to cold weather did not increase whereas SEA and PMM alone groups both had their pain further worsened by cold weather; and 2) CM heat pattern reported improved sensitivity to hot packs in alleviating their pain after REA. These may perhaps be due to acupuncture increased surface temperature [1094]. An OM review found OM induced hyperthermia/hypothermia depending on the animal species and the dose of OM, where high dose of OM induced hypothermia and low dose of OM induced hyperthermia [1095]. The baseline comparison showed no statistically significant difference between the three treatment groups in OM consumption (Table 8.6) nor was there any difference when the two CM patterns were compared (Appendix 29). How much this non-sensitivity to cold temperature was due to the

effect of REA and the better response in pain alleviated by “hot packs” due to REA within CM heat pattern is unknown due to small sample size. The mechanism of this new information awaits further research to identify.

8.4.6 Interpretation of findings – other symptoms

For the two CM patterns, due to small sample size and uneven distribution of symptoms amongst the two patterns and the three treatment groups, it was not possible to identify which pattern responded best to REA.

Table 8.15 Comparison of significant changes between baseline and end of treatment weeks amongst the three treatment groups and their baseline week data

Domain	Sub-categories	Item	Treatment group and changes					
			REA (n=27)		SEA (n=22)		PMM alone (n=17)	
			Significant changes	Number of baseline week yes	Significant changes	Number of baseline week yes	Significant changes	Number of baseline week yes
Pain regions	Upper limb	Upper arm+	NS	6	I	12	NS	4
		Forearm+		2		8		1
	Front of the body	Side of the body		3	D	3		0
	Back of the body	Between shoulder blades		9	NS	10	D	3
		Sacrum		8	I	7	NS	6
Pain quality	&	Numbness		10	NS	9	I	7
		Fixed location		12	I	13	NS	6
Pain aggravators	Environmental changes	Cold weather		15	D	10	D	8
	Exercises or sporting	Any movement		6	NS	6	I	6
Pain alleviators	Environmental changes	Warm/hot shower		9		11	I	5
	Physiological and psychic changes	Reading		4	I	2	NS	3
		Keeping my mind off pain		11		5		7
	Other	Nothing	I	5	NS	2		1
Other symptoms	&	Nausea	I	8	I	9		2
		Dizziness	NS	6		9		5
		Poor appetite		9		8		5
		Poor memory		10	NS	11	I	12

+Indicates significant difference between groups in baseline week

Shaded item means improvement seen in one group but one of the other two groups has less than four participants having such item in baseline week. Such rule also applies to “nothing” in pain alleviator but does not apply to the rest of the pain alleviator.

& no sub category for pain quality and other symptoms

D: Deterioration; I: Improvement; NS: Not significant;

REA: Real electro acupuncture; SEA: Sham electro acupuncture; PMM alone: Pain medication management alone

Table 8.16 Comparison of significant changes between baseline and end of treatment weeks amongst the CM heat pattern (cluster four) and the CM "cold with deficiency" pattern (cluster five) and their baseline week data

Domain	Sub-categories	Item	Treatment group and changes											
			REA (n=21)				SEA (n=21)				PMM alone (n=15)			
			Cluster 4 (n=13)		Cluster 5 (n=8)		Cluster 4 (n=11)		Cluster 5 (n=10)		Cluster 4 (n=6)		Cluster 5 (n=9)	
			S. C.	Number of baseline week yes	S. C.	Number of baseline week yes	S. C.	Number of baseline week yes	S. C.	Number of baseline week yes	S. C.	Number of baseline week yes	S. C.	Number of baseline week yes
Pain region	Lower limb	Calf	NS	1	NS	3	I	6	NS	0	NS	1	NS	3
		Front of the leg+		0		1		7		2		0		4
Pain quality	&	Fixed location		4	I	7	NS	4	I	8		3		3
		Numbness		6	NS	1		4	NS	4		2	I	4*
Pain rhythm	&	All the time		8		7	I	9		8		5	NS	4
		Worse when first get up	I	6		4	NS	2		3		2		3
Pain aggravator	Environmental changes	Cold weather	NS	6		5	D	5	D	4	NS	3	D	5
Pain alleviator	Environmental changes	Hot packs+	I	3		5	NS	5	NS	9		2	NS	5
	Other	Keeping busy	NS	3		3		2	I	3		3		1
Other symptoms	&	Swollen joints		1		2		5		4*		3		0
		Dry stools+		0		0		0		4*		0		1
		Poor appetite+		3		3	I	4*	NS	4		0		5
		Nausea		2		4		5*		4		1		1
		Dizziness+		1		2	NS	2	I	6		1		4

S.C.: Significant changes

[+]Indicates significant difference between groups in baseline week
*indicates participants who had the symptom all improved from this symptom.
Shaded item means improvement seen in one group but one of the other groups has less than four participants having such item in baseline week. Such rule does not apply to pain alleviator.
& no sub category for pain quality and other symptoms
D: Deterioration; I: Improvement; NS: Not significant;
REA: Real electro acupuncture; SEA: Sham electro acupuncture; PMM alone: Pain medication management alone

8.4.7 Comparison with other OM studies

When compared with other opioid detoxification researches, they used different outcome measures to CMPQ and included pain severity subscale of the Multidimensional Pain Inventory and Center for Epidemiologic Studies–Depression scale [1096] or cold pressor to assess pain tolerance [1097]. The pain severity subscale of the Multidimensional Pain Inventory focuses on the severity of pain at present, in the last week, as well as the severity of suffering due to pain. The uniqueness of CMPQ was in assessment of complete disappearance of symptoms whereas the other three assessments were on a scale and focused on changes in severity, and the spectrum of symptoms covered in CMPQ, included the six domains (refer to Chapter 5 CMPQ item generation (p. 152)), was far greater than any of the three assessments mentioned. Especially the accompanying symptom domain which focuses on the other physical and mental symptoms. This domain is linked through the CM theory and is unique to CM.

Limitations of the study:

1) Sample size was small for all three groups. This was due to that patients did not want to reduce OM. Within the EAOM trial, 556 potential participants met the inclusion criteria and only 151 consented to participate the trial. The dropout from the EAOM trial made the sample size even smaller and intention to treat analysis was not applied. Although the sample size was small, the differences between them in the changes within the treatment group and the clusters via Cochran's Q test were significant ($p<0.05$). The association between the CM patterns, SF36, and BDI were also significant taking Bonferroni correction into consideration. Potentially there were differences between the CM patterns in QoL and depression. Such possibility awaits further research in the CM heat pattern and the CM "cold with deficiency" pattern type participants.

2) Variability of the CMPQ data was limited by the dichotomous format. Such format limited the assessment of changes although the presence/absence of a symptom was the basis of CM diagnosis.

3) The EAOM trial treatment protocol was limited to four main points to induce the release of endorphin plus other points to address the side effect of OM. This method was not commonly used in acupuncture practice and the results from the treatment did not represent

the common practice [136(p14-21)]. The REA treatment effect on CMPQ is thus limited to this type of protocol.

Implication for research

Based on the results of the study, CMPQ may be able to reflect changes after acupuncture treatments. Further studies with large sample size, more variety of CMP, likert-scaled response in CMPQ, are recommended for evaluating the differences between the two clusters of CMP patients who take OM for pain control.

Implication for clinical practice

Chinese medicine pattern identification can further sub-group CMP despite of their similarities in OM consumption and pain intensity and may help assess changes in clinical presentation. The two CM patterns provide additional indicators of change, such as if pain can be relieved by hot pack, and if pain is aggravated by cold weather. The significance of such information is meaningful to CM practitioners.

9. General discussion and Conclusion

9.1 Summary of findings

The objectives of the project included 1) identifying the comorbidities and symptomatologies of CMP through a SR; 2) developing and validating a CMPQ for pattern identification in CMP patients who are OM users; 3) differentiating the CM patterns of CMP who use OM for pain control using cluster analysis; and determine the cluster differences in demography, pain intensity and OM consumption, depression, QoL, and disability; and 4) determining the differences between patterns and clinical outcomes of EA based on the change in CMPQ symptoms, pain intensity, OM consumption, depression, and QoL.

9.1.1 The Systematic review

Seventy two English studies were identified in the SR through searches in English databases. Overall, the finding reflected high associations between CMP and comorbidities and/or accompanying symptoms, particularly the association between chronic SP and other types of pain (such as headache, migraine, chronic back or neck pain, arthritis, or other chronic pain) (OR 1.33-7.9), and the association between arthritis and heart diseases/symptoms (OR 3.1-8.7). Overall the SR showed a high association between CMP and mental disorders (OR 1.48 - 6.2) and headache/migraine (OR 1.33 – 7.0).

9.1.2 Development of CMPQ

The development of CMPQ included the literature review, item generation, and internal group discussion. The resultant CMPQ contained 187 items grouped into six domains. These items could be understood from the CM perspective and formed CM patterns.

9.1.3 The essential properties of CMPQ

The CMPQ demonstrated good face and content validities, test-retest reliability (correlation coefficient=0.846 for overall questionnaire, and above 0.7 for all domains except for the pain quality and pain rhythm domain where the correlation coefficients were between 0.49-0.556), and internal consistency (Cronbach's α=0.931). Items related to OM side effects were assessed for responsiveness. Of these items, bowel movement as pain alleviator and skin itch as accompanying symptom showed responsiveness to REA and there was no symptom responding to PMM alone.

9.1.4 Clusters of CMP and CM interpretation of the clusters

The current study identified two main clusters and their corresponding CM patterns. They were CMP due to heat pattern (cluster four) and CMP due to "cold with deficiency" pattern (cluster five). The CM patterns were different from the ones listed in the textbooks [132(p706-708,890-895) 1022(p963,973,976,984,987,995,996,1002,1005,1007,1012,1014,1017,1019,1023,1032,1034,1042,1045,1047,1051,1054,1062,1069,1078,1094,1097,1107,1108,1116,1131,1136,1158,1168,1171,1172,1176,1177,1306,1325,1536,1538,1541-1548,1554-1557,1567-1570,1574-1576,1579-1581,1583,1584,1586-1588,1631-1635,1642-1644,1650-1651,1652-1653,1654-1656)1020(p981-1047,1059-1118)1021(p308-335)]. The grouping of CMP sub types was by scientifically sound factor and cluster analyses and data from real patients rather than expert opinion or data from uncertain sources as described in the CM classics. Using cluster analysis to group symptoms had been used in CM pattern research [1050,1098].

9.1.5 Association with other outcome measures

The study had found CM heat pattern (cluster four) was associated with better overall QoL and mild depression whereas CM "cold with deficiency" pattern (cluster five) was associated with the worse overall QoL and moderate depression.

9.1.6 Evaluating effects of treatments on the symptoms of participants

The CMPQ was able to detect minor changes amongst the three treatment groups. The CMPQ showed REA was the only group that did not show symptom deterioration. On the other hand, SEA showed the most improvement in symptoms followed by REA and PMM alone. Real EA was the only group that showed no deterioration in pain worsened by cold weather whereas SEA and PMM alone both had deterioration in response to cold weather.

9.1.7 Effect of treatment on subgroups and outcome measures

Chinese medicine heat pattern (cluster four) responded to REA with a slightly better result as fewer participants reported their pain became worse when they first got up and more participants felt that hot packs alleviated their pain when compared with the CM "cold with deficiency" pattern which showed improvement in pain at fixed location only. There was no pattern that responded best to REA. Only OM consumption and BDI improved over time without group differences. There were no statistical significant changes associated with the two clusters and the three treatment groups over time for QoL and average pain intensity.

9.2 Strengths and limitations of the project

9.2.1 Strengths of the project

9.2.1.1 A holistic view of CMP

The SR, to the best knowledge of the authors, is the first to systematically evaluate the comorbidities/accompanying symptoms of CMP that was not limited to a particular kind of CMP such as LBP or arthritis. The approach views CMP from a holistic approach instead of the individual type of CMP alone. In comparison to previous SRs on comorbidities, this SR has more included studies (n=72), whereas prior studies included 16 studies on LBP and respiratory disorders [1099]. The SR also identified the common comorbidities amongst chronic SP and arthritis and the association between arthritis and chronic SP.

9.2.1.2 The CM evaluation process

Based on the author's knowledge, this is the first study to evaluate the effect of treatment from a CM perspective by using CMPQ for CMP who take OM for pain control. The multidimensionality of CMPQ enables the assessment of a much broader range of symptoms. Many changes are not captured by simply assessing the intensity of pain, OM consumption, SF36, and BDI. For instance, the accompanying nausea, dizziness, poor appetite, poor memory, reduction in the number of painful sites, the change in painful sensation (e.g. numbness to less numbness), and the increased/decreased sensitivity towards cold weather are common presentations of CMP, but are not captured using the standard assessment tools. To the best knowledge of the author, evaluating outcomes from a CM perspective was not utilised in pain management centres in Melbourne, Victoria, Australia. Without detailed evaluation 1) treatment effects may not be fully captured in a pain management centre; and 2) treatments may not be tailored to each individual patient. See further discussion in Chapter 9.5 Preliminary effect of treatment on subgroup of participants (p. 305).

9.2.1.3 The two distinctive and meaningful patterns of CMP who use OM for pain control

In addition, the current study also identified the two key CM subgroups of CMP i.e. Chinese

medicine heat pattern and CM cold with deficiency pattern. More importantly the two meaningful patterns were identified based on advanced statistical analyses (factor analysis and cluster analysis) combined with experts' opinions rather than the latter alone which is the approach that has been used in textbooks. The CM heat pattern and CM cold with deficiency pattern differ in their nature- the CM heat pattern includes "red and hot joints, palms, and face", and skin itch whereas the CM cold with deficiency pattern includes cold extremities, feeling cold easily, poor concentration/memory/appetite, low libido, dizziness, stuffiness in the chest, shortness of breath, night sweating, feeling tired easily, and catching cold easily. These two distinct subgroups also differed in their QoL and depression. Chinese medicine heat pattern shows less severe depression and better QoL when compared with CM cold with deficiency pattern.

Other studies have also identified cold and heat patterns in RA. Metabonomically, the cold pattern of RA may have higher rates of fat and protein mobilization, whereas for the heat pattern, the oxidative stress and collagen destruction may be more severe [1100]. Chinese medicine heat pattern is associated with elevated plasma concentrations of glycochenodeoxycholate, proline, saturated and mono-unsaturated phosphatidylcholine but decreased levels of urea, free fatty acid and polyunsaturated phosphatidylcholine [1100]. Furthermore, CM cold and heat patterns of RA were associated with 29 and 19 differential metabolites respectively [1101]. The common metabolites involved in both CM patterns were perturbation of amino acid metabolism, carbohydrate metabolism and lipid metabolism. Specifically, metabolic perturbations in protein and collagen breakdown, decreased glycolytic activity and aerobic oxidation, and increased energy utilization were associated with CM cold pattern but not in the CM heat pattern [1101]. These findings support the differences between the CM cold pattern and CM heat pattern at the molecular level and from the metabolic perspective. These information further support the usefulness of CM knowledge in differentiating syndromes and identifying sub-groups of CMP.

9.2.1.4 A rapid and simplified CM pattern identification process

The CMPQ items were designed based on the CM eight guiding principles. This method enabled quick CM pattern identification. Based on the CM patterns identified, a practitioner can select the appropriate treatment for the CMP patients. Whether using acupuncture only or using moxibustion concurrently, the practitioner needs to treat patients based on the CM pattern identified for a better outcome [1102].

9.2.2 Limitations of the project

9.2.2.1 Language restriction in SR

The SR included only English literature and no Chinese literature was found in the English database searches. Literature in other languages were excluded. Egger et al. argued English literatures tended to show statistical significant results and excluding non-English literatures produced a biased results [1103]. However, Morrison et al. investigated the effect of English and non-English literatures on systematic review and found no systematic bias from the use of English language restriction [1104]. Including only English language studies in the SR should not impact on the validity of the results.

9.2.2.2 Low NOS score in SR

The quality appraisal was assessed with NOS. The low score of the NOS limited the interpretability of the results. For this reason, findings were only confirmed if more than one study reported the same results as the chance for multiple studies to report the same false association is low.

9.2.2.3 Limitation of the SR data

The design of the SR did not allow for the causal relationship evaluation. It is not possible to ascertain whether the comorbidities/accompanying symptoms caused the CMP, vice versa, or they are simply just associated with each other. It will be helpful to identify the nature of the relationship or mechanisms underlying these co-existing diseases/accompanying symptoms for the better treatment/management of the patient's overall health.

9.2.2.4 Number of non-menopausal females was limited

The majority of the included female participants were at the post-menopausal stage (69% of females, 42 out of 56 females). Such a small sample may produce random error if the data on gynaecological symptoms (such as menstrual cycle related symptoms or vaginal discharges) were taken into consideration when cluster analysis was used [1105]. These gynaecological symptoms were subsequently removed in factor and cluster analysis to prevent distortion of the factors and clusters.

9.2.2.5 Dichotomous outcome

The dichotomous response limited the flexibility of changes. Participants who only had mild improvement would not show changes. Only significant changes from presence to absence or vice versa of a symptom would show changes.

9.2.2.6 Small sample size

The sample size was relatively small, but sufficient for assessing the validities and reliabilities. When the sample was divided into treatment groups and when drop outs were taken into consideration, the sample size became smaller for each group, varying from 28 to 45 at week five, and 17 to 28 at end of treatment week. Although such a small sample size may lead to random error when evaluated the treatment effects [1105], the statistical significance level was adjusted for small sample size.

9.3 CM pattern identification and subgroups of CMP

This project used factor and cluster analysis to group the symptoms. Both statistical methods have been used in both CM and western medicine to sub-group symptoms within a disease/condition [1016,1053]. When identifying the patterns of symptom cluster, it is necessary to engage CM experts to evaluate the symptoms. The advantage of evaluating the patterns using CM knowledge is that the existing CM theory explains the complex relationship between and among the symptoms. Furthermore, there are existing treatment principles and treatments for each pattern.

In comparison to the modern textbook, differences exist between the current finding and the textbooks [132(p890-895)]. The 10 types of CM patterns for Bi syndrome are, wind dampness Bi obstruction (风湿痹阻), cold dampness Bi obstruction (寒湿痹阻), cold and heat mixture (寒热错杂), damp heat Bi obstruction (湿热痹阻), heat toxin Bi obstruction (热毒痹阻), static blood Bi obstruction (瘀血痹阻), phlegm turbidity Bi obstruction (痰浊痹阻), phlegm stasis Bi obstruction (痰瘀痹阻), deficiency of both Qi and Yin (blood) (气阴(血)两虚), deficiency of both CM liver and CM kidney (肝肾两虚) [132(p890-895)]. Bi syndrome, as explained in Chapter 2.6.3 How does CM view and differentiate CMP (p. 36), includes pain in the joint/muscle/bone/tendon, and is consistent with the painful regions of the recruited participants. The possible reasons for the differences between the results of the current project and the

textbooks may be the use of OM, the use of factor and cluster analysis, and the use of the CM eight guiding principles. Due to long term consumption of OM, which is a restricted medication [1106], the participants in the current study were very specific whereas the patients described in the textbook were more general and would less likely have included any symptoms associated with the use of OM. As previously reported, the methods of CM pattern identification used in the textbooks about Bi syndrome were the combination of six pathogenic factor diagnosis, Qi blood and body fluid diagnosis, and CM Zang Fu pattern identification (Table 9.1), but not the CM eight guiding principles method of diagnosis. The CM eight guiding principles diagnosis is the leading pattern identification method and classifies all patterns into six key patterns (cold versus heat, deficiency versus excess, interior versus exterior) with two overarching categories (Yin and Yang). It is used to re-classify and simplify patterns identified using other methods. For this reason, it is more appropriate and easier to research sub-groups of CMP using the CM eight guiding principles as a starting point.

Table 9.1 Methods of CM pattern identification for Bi syndrome

CM pattern identification	**Six pathogenic factor diagnosis**	**Qi blood and body fluid diagnosis**	**CM Zang Fu pattern identification**	**CM eight guiding principles diagnosis**
Wind dampness Bi obstruction (风湿痹阻)	x			Cold, excess, exterior
Cold dampness Bi obstruction (寒湿痹阻)	x			Cold, excess, exterior
Cold and heat mixture (寒热错杂)				Cold and heat
Damp heat Bi obstruction (湿热痹阻)	x			Heat, excess, interior
Heat toxin Bi obstruction (热毒痹阻)	x			Heat excess, interior
Static blood Bi obstruction (瘀血痹阻)		x		Excess, interior
Phlegm turbidity Bi obstruction (痰浊痹阻)		x		Excess, interior
Phlegm stasis Bi obstruction (痰		x		Excess, interior

CM pattern identification	Six pathogenic factor diagnosis	Qi blood and body fluid diagnosis	CM Zang Fu pattern identification	CM eight guiding principles diagnosis
瘀痹阻),				
Deficiency of both Qi and Yin (blood) (气阴(血)两虚)		x		Deficiency, interior
Deficiency of both CM liver and CM kidney (肝肾两虚)			x	Deficiency, interior

Information extracted from [132(p890-895)]
CM: Chinese medicine

Discrepancies in textbook patterns and those identified in research also exist in other study that used factor and cluster analysis to research fatty liver [1060]. According to the CM textbook, and a CM and western medicine integrated book on liver disease [1107(p221)132(p863-866)], fatty liver is similar to accumulation syndrome (积聚) in CM and has the following CM patterns; 1) Qi stagnation and dampness obstruction (气郁湿阻), 2) phlegm and Qi mutual stagnation (痰气互结) 3) Qi stagnation and blood stasis (气滞血瘀) 4) CM liver stagnation and Qi stagnation (肝郁气滞), 5) food turbidity obstruction and stagnation (食浊阻滞) 6) heat stagnation and Fu organ excess(热结腑实) 7) Qi and blood obstruction and stagnation (气血阻滞), 8) Qi knotting and blood stasis (气结血瘀), 9) damp heat knotting with toxins (湿热结毒) 10) antipathogenic factor deficiency with stagnation and stasis (正虚瘀结). The finding from the fatty liver study (n=793) [1060] resulted in however seven clusters. The authors evaluated the symptoms within the clusters and diagnosed five out of seven of them with 1) retention of phlegmatic dampness due to CM spleen deficiency (脾虚痰湿中阻) (32.0%), 2) Yin deficiency of CM liver and CM kidney (肝肾阴虚) (18.5%), 3) phlegm accumulating with stagnation due to CM spleen deficiency (脾虚痰瘀互结) (11.5%), 4) internal accumulation of damp-heat due to CM spleen deficiency (脾虚湿热内蕴) (10.2%), and 5) dampness obstruction due to CM liver Qi stagnation and CM spleen deficiency (肝郁脾虚湿阻) (8.3%). The remaining two clusters were asymptomatic (13.6%), and CM pattern-uncategorizable (5.8%). This clinical study showed a combination of excess and deficiency patterns with CM organ involvements instead of just the excess, deficiency, or a combination of them. The authors listed the signs and

symptoms within the clusters and labelled them with CM patterns. Such discrepancy illustrates the differences between theory and reality. Reality is more important than theory. When in reality, the CM heat and CM cold with deficiency patterns are more predominant, both patterns deserve more attention. In clinical practice, it is more important to focus on these patterns than rarely occurring patterns such as cluster one and three (n=1 each, 1%) in Chapter 7.3.3 Cluster analysis (p. 236). Chinese medicine textbook information needs to be evidence-based. If the CM textbook based on experts' opinion differs from research data, revisions of the textbook are then required. If the textbook contains symptoms that are rarely occurring, such as "windy day" as pain alleviator, it should be acknowledged in the textbook. More research in CM pattern identification reflecting the health conditions in reality is needed.

9.4 Effect of treatment captured by CMPQ

The effect of treatment captured by CMPQ indicated 1) CMPQ as an outcome measure was able to capture treatment effects that were not detectable using other outcome measures in the three treatment groups, and 2) REA group had no symptom deterioration and two symptom improvements, SEA group had two symptom deteriorations with nine symptom improvements and PMM alone group had two symptom deteriorations and four symptom improvements. Such noticeable differences were not captured by simply examining the OM consumption, average pain, SF36, and BDI. Such differences are less likely due to different degrees of OM reduction among the three groups given all groups reduced OM dosages without any statistically significant differences. It is important to note the difference captured by CMPQ was within groups, but not between groups. The between group analysis was not made because there were excessive numbers of comparisons (CMPQ has 163 main items for comparison) and multiple baseline incomparabilities. Due to small sample size and the multiple incomparabilities between the treatment groups, caution is advised when interpreting the treatment results.

Another method of comparison between treatments is by comparing the number of symptoms recorded at different time points. Such an approach is used in SF36 and McGill Pain Questionnaire [1024]. Chinese medicine pain questionnaire could follow this method which is meaningful to both the patients and from the statistics perspective. Future development could incorporate the likert scale and this summing up the number of symptoms approach to compare the treatment results.

9.5 Preliminary effect of treatment on subgroup of participants

In CM, the treatments strategy for the two patterns identified should differ [136(p5-15)]. For CM heat pattern, clearing heat method should have been used and for CM "cold with deficiency" pattern, warming and tonifying methods should be adopted. In acupuncture practice, applying filiform needles or blood letting using three edge needle are used to treat CM heat pattern whereas filiform needling and moxibustion treatment are prescribed for CM "cold with deficiency" pattern [136(p3)]. Overall, CM heat pattern, with statistical significant improvement for two symptoms, performed slightly better than CM "cold with deficiency" pattern, with statistical significant improvement for one symptom, as assessed in CMPQ. Part of the reason may be the study protocol did not take the individualised treatment into consideration. In the EAOM trial, only EA was used without moxibustion. That is, the trial acupuncture protocol might be more appropriate for subjects with the CM heat pattern.

Brinkhaus et al. identified five groups of CM patterns in LBP patients based on the individual doctor's CM pattern identification [1108]. They were 1) Bi syndrome patterns (24%), including Bi syndrome, cold, damp, heat, and wind patterns; 2) Qi and blood stagnation patterns (24%), including Qi and blood stagnation, blood stagnation, and Qi stagnation which also included CM liver Qi stagnation; 3) CM kidney deficiency patterns (34%), including general CM kidney deficiency, CM kidney Yang deficiency, CM kidney Yin deficiency, and CM kidney Qi deficiency; 4) CM liver and CM spleen Qi deficiency patterns (6%), including CM liver Qi deficiency, and CM spleen Qi deficiency; and 5) other diagnosis (11%). Such diverse CM patterns require different approaches to treat them according to CM principles. Their treatment results were published separately and involved comparing acupuncture, minimal acupuncture, and UC treatments [1109]. Their acupuncture treatment was based on local and distal points without taking CM pattern identification into consideration. The trial acupuncturist could use additional ear points/trigger points/other points. Minimal acupuncture utilised different points and shallow needling. They found acupuncture was better than UC in improving pain and there was no significant difference between acupuncture and minimal acupuncture. Another acupuncture study by Cherkin et al. [1110] compared standardised acupuncture, individualised acupuncture, sham acupuncture, and UC. This study did not report the CM patterns of the participants. From both Brinkhaus's and MacPherson's studies (MacPherson's study was formerly described in Chapter 7.4.2 CM patterns: heat and cold patterns (p. 254)) [1065,1108], it is clear the deficiency pattern and cold pattern exist in LBP. Cherkin had found no difference between standardised and individualised acupuncture and having any kind of acupuncture

treatment was better than UC. Neither Brinkhaus nor Cherkin mentioned the use of moxibustion. This may be the reason why there was no difference between acupuncture and minimal/sham acupuncture, and no difference between individualised and standard acupuncture treatment. An individually tailored treatment incorporating moxibustion or heat therapy when indicated may provide a better outcome for the individualised acupuncture treatment. Research in acupuncture clinical studies should focus on developing acupuncture treatments for CM heat pattern and CM cold pattern separately rather than a fixed acupuncture treatment protocol without incorporating moxibustion to enhance the acupuncture treatment outcome.

9.6 Implications for future research

Based on the current project, the following recommendations are made:

1) Further research on CMPQ validation is recommended for there were changes associated with treatments not captured in other outcome measures.

2) Conduct a larger study involving more varieties of CMP, focusing on CM heat pattern and CM cold with deficiency pattern participants with and without taking OM for their pain control are required to further evaluate the validity and reliability of CMPQ.

3) It is also necessary to modify CMPQ to enable identification of the effects of treatment of these two CM patterns. Changing the dichotomous outcome format to likert scale in CMPQ will enable a better assessment of the changes in patients. This will help better understand the treatment effect on patients, and provide a scoring method for treatment effect comparison. The rarely selected items should be removed. Like other questionnaire developments, this is the first step in developing CMPQ. More adjustments and developments are needed before CMPQ can be used as an outcome measure in clinical trials.

4) The patterns identified need to be considered when designing future acupuncture clinical trials.

9.7 Implications for clinical practice

In clinical practice, it is proposed that CMP patients be assessed using a holistic approach in which the comorbidities and/or accompanying symptoms are assessed together. This may help in identifying whether patients have other major health problems. Patients should be informed of the comorbidities that are highly associated with their disorder, for instance, the high risk of comorbidities such as hypertension and heart attack in chronic SP/arthritis patients. Preventative measures/advice should be implemented to improve the overall wellbeing of patients. Routine screening/check-ups for those high-risk comorbidities should be conducted periodically for CMP patients.

Currently this version of CMPQ still needs further research in order to ensure its criterion and construct validities and inter rater reliability. Further revision is also required to improve the content of CMPQ. It is not suitable as the sole means of patient case history collection and CM pattern identification. Instead, the revised version of CMPQ can be used by western medicine doctor to understand the multi-dimensionality of CMP symptom presentation, leading to a better understanding of a total picture of the patients, including pain and non-pain presentation.

References

1. Xue CC, Helme RD, Gibson S, Hogg M, Arnold C, Somogyi AA, et al. Effect of electroacupuncture on opioid consumption in patients with chronic musculoskeletal pain: protocol of a randomised controlled trial. Trials. 2012;13:169. doi: 10.1186/1745-6215-13-169
2. Kuttikat A, Shenker N. Pharmacological modulation of central nociception in the management of chronic musculoskeletal pain. Pain Management. 2011 2011/11/01 [cited 2013/11/02];1(6):549-556. doi: 10.2217/pmt.11.63
3. Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. Pain. 2001 Jan;89(2-3):127-34.
4. van der Windt DA, Dunn KM, Spies-Dorgelo MN, Mallen CD, Blankenstein AH, Stalman WA. Impact of physical symptoms on perceived health in the community. J Psychosom Res. 2008 Mar;64(3):265-74. doi: 10.1016/j.jpsychores.2007.10.003
5. Veale DJ, Woolf AD, Carr AJ. Chronic musculoskeletal pain and arthritis: impact, attitudes and perceptions. Ir Med J. 2008 Jul-Aug;101(7):208-10.
6. Martimo KP, Shiri R, Miranda H, Ketola R, Varonen H, Viikari-Juntura E. Self-reported productivity loss among workers with upper extremity disorders. Scand J Work Environ Health. 2009 Jul;35(4):301-8.
7. de Lissovoy G, Brown RE, Halpern M, Hassenbusch SJ, Ross E. Cost-effectiveness of long-term intrathecal morphine therapy for pain associated with failed back surgery syndrome. Clin Ther. 1997 Jan-Feb;19(1):96-112; discussion 84-5.
8. Access Economics Pty Limited. The high price of pain: the economic impact of persistent pain in Australia2007: Available from: http://www.bupa.com.au/staticfiles/BupaP3/Health%20and%20Wellness/MediaFiles/PDFs/MBF_Foundation_the_price_of_pain.pdf.
9. Hunt T. Pain In Europe – A Report. [cited 2013 02/11/2013]. Available from: http://www.paineurope.com/docs/default-source/default-document-library/openminds-pain-in-europe-survey.pdf
10. Hall A, Maher C, Latimer J, Ferreira M. The effectiveness of Tai Chi for chronic musculoskeletal pain conditions: a systematic review and meta-analysis. Arthritis Rheum. 2009 Jun 15;61(6):717-24. doi: 10.1002/art.24515
11. International Association for the Study of Pain (IASP). Global year against musculoskeletal pain, October 2009–October 2010 [cited 2013 03/11/2013]. Available from: http://www.iasp-pain.org/AM/Template.cfm?Section=2009_2010_Musculoskeletal_Pain&Template=/CM/HTMLDisplay.cfm&ContentID=9310
12. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015 Jun;156(6):1003-7. doi: 10.1097/j.pain.0000000000000160
13. Office of Communications and Public Liaison. Pain: Hope Through Research. National Institute of Neurological Disorders and Stroke; 2014 [cited 2015 09/07/2015]. Available from: http://www.ninds.nih.gov/disorders/chronic_pain/detail_chronic_pain.htm
14. Rice DP, LaPlante MP. Medical expenditures for disability and disabling comorbidity. Am J Public Health. 1992 May;82(5):739-41.
15. Caughey GE, Vitry AI, Gilbert AL, Roughead EE. Prevalence of comorbidity of chronic diseases in Australia. BMC Public Health. 2008;8:221. doi: 10.1186/1471-2458-8-221
16. Carstensen J, Andersson D, Andre M, Engstrom S, Magnusson H, Borgquist LA. How does comorbidity influence healthcare costs? A population-based cross-sectional study of depression, back pain and osteoarthritis. BMJ Open. 2012;2(2):e000809. doi: 10.1136/bmjopen-2011-000809
17. Kim H, Lee J. The impact of comorbidity on wealth changes in later life. J Gerontol B Psychol Sci Soc Sci. 2006 Nov;61(6):S307-14.
18. Xuan J, Kirchdoerfer LJ, Boyer JG, Norwood GJ. Effects of comorbidity on health-related quality-of-life scores: an analysis of clinical trial data. Clin Ther. 1999 Feb;21(2):383-403. doi: 10.1016/S0149-2918(00)88295-8
19. Bosc M. Assessment of social functioning in depression. Compr Psychiatry. 2000 Jan-Feb;41(1):63-9.
20. Peat G, Thomas E, Wilkie R, Croft P. Multiple joint pain and lower extremity disability in middle and old age. Disabil Rehabil. 2006 Dec 30;28(24):1543-9. doi: 10.1080/09638280600646250
21. Guideline for the non-surgical management of hip and knee osteoarthritis. South Melbourne: The Royal Australian College of General Practitioners College House; 2009 [cited 23/07/2012]. Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp117-hip-knee-osteoarthritis.pdf
22. World Health Organization. WHO's pain ladder for adults. World Health Organization [cited 2013 18/09/2013]. Available from: http://www.who.int/cancer/palliative/painladder/en/
23. The Pain & Policy Studies Group. Australia | Pain & Policy Studies Group. [cited 2016 01/12/2016]. Available from: http://www.painpolicy.wisc.edu/country/profile/australia
24. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia.

Med J Aust. 2011 Sep 05;195(5):280-4.
25. Gowing L, Ali R, Dunlop A, Farrell M, Lintzeris N. National Guidelines for Medication-Assisted Treatment of Opioid Dependence2014: Available from: http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/AD14DA97D8EE00E8CA257CD1001E0E5D/$File/National_Guidelines_2014.pdf.
26. Mattia C, Coluzzi F. COX-2 inhibitors: pharmacological data and adverse effects. Minerva Anestesiol. 2005 Jul-Aug;71(7-8):461-70.
27. Patrono C, Baigent C. Nonsteroidal anti-inflammatory drugs and the heart. Circulation. 2014 Feb 25;129(8):907-16. doi: 10.1161/CIRCULATIONAHA.113.004480
28. Chrousos GP. Adrenocorticosteroids & Adrenocortical Antagonists. In: Katzung BG, Masters SB, Trevor AJ, editors. Basic and clinical pharmacology. 12th ed. New York : London: McGraw-Hill Medical; 2012 p.697-713.
29. Boutayeb A, Boutayeb S, Boutayeb W. Multi-morbidity of non communicable diseases and equity in WHO Eastern Mediterranean countries. Int J Equity Health. 2013;12:60. doi: 10.1186/1475-9276-12-60
30. Huang CQ, Dong BR, Lu ZC, Yue JR, Liu QX. Chronic diseases and risk for depression in old age: a meta-analysis of published literature. Ageing Res Rev. 2010 Apr;9(2):131-41. doi: 10.1016/j.arr.2009.05.005
31. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). Saudi Pharm J. 2014 Apr;22(2):83-94. doi: 10.1016/j.jsps.2013.02.003
32. National Guideline Clearinghouse. Chronic pain disorder medical treatment guidelines2011: Available from: https://www.guideline.gov/summaries/summary/38441?
33. Kalavapalli R, Singareddy R. Role of acupuncture in the treatment of insomnia: a comprehensive review. Complement Ther Clin Pract. 2007 Aug;13(3):184-93. doi: 10.1016/j.ctcp.2007.01.001
34. Taylor P, Pezzullo L, Grant SJ, Bensoussan A. Cost-effectiveness of Acupuncture for Chronic Nonspecific Low Back Pain. Pain Pract. 2014 Sep;14(7):599-606. doi: 10.1111/papr.12116
35. Vickers AJ, Cronin AM, Maschino AC, Lewith G, MacPherson H, Foster NE, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med. 2012 Oct 22;172(19):1444-53. doi: 10.1001/archinternmed.2012.3654
36. Gadau M, Yeung WF, Liu H, Zaslawski C, Tan YS, Wang FC, et al. Acupuncture and moxibustion for lateral elbow pain: a systematic review of randomized controlled trials. BMC Complement Altern Med. 2014;14:136. doi: 10.1186/1472-6882-14-136
37. Green S, Buchbinder R, Hetrick S. Acupuncture for shoulder pain. Cochrane Database Syst Rev. 2005 (2):CD005319.
38. Deng TT. Traditional Chinese Medicine Diagnosis [中医诊断学]. Shanghai Science Technology Press (上海科学技术出版社); 1984.
39. Hartvigsen J, Natvig B, Ferreira M. Is it all about a pain in the back? Best Pract Res Clin Rheumatol. 2013 Oct;27(5):613-23. doi: 10.1016/j.berh.2013.09.008
40. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009 Jul 21;6(7):e1000100. doi: 10.1371/journal.pmed.1000100
41. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited 2013 13/12/2013]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
42. WHO. International Classification of Diseases (ICD)2010: Available from: http://www.who.int/classifications/icd/en/.
43. International Association for the Study of Pain (IASP). IASP Taxonomy - IASP. IASP [28/11/2016]. Available from: http://www.iasp-pain.org/Taxonomy
44. NPS MedicineWise. Chronic pain: definition | NPS MedicineWise. [cited 2016 28/11/2016]. Available from: http://www.nps.org.au/conditions/nervous-system-problems/pain/for-individuals/pain-conditions/chronic-pain/for-individuals/what-it-is
45. Anderson DM, Keith J, Novak PD. Mosby's medical, nursing, & allied health dictionary. 6 ed. Missouri: A Harcourt Health Sciences Company; 2002.
46. WHO. International Classification of Diseases (ICD)2007: Available from: http://www.who.int/classifications/icd/en/.
47. March LM, Brnabic AJ, Skinner JC, Schwarz JM, Finnegan T, Druce J, et al. Musculoskeletal disability among elderly people in the community. Med J Aust. 1998 May 4;168(9):439-42.
48. Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D. Localized or widespread musculoskeletal pain: does it matter? Pain. 2008 Aug 15;138(1):41-6.
49. Bingefors K, Isacson D. Epidemiology, co-morbidity, and impact on health-related quality of life of self-reported headache and musculoskeletal pain - A gender perspective. European Journal of Pain. 2004;8(5):435-450. doi: 10.1016/j.ejpain.2004.01.005

50. Abusdal UG, Hagen KB, Bjorndal A. [Self-reported chronic muscle pain among women in Oslo]. Tidsskr Nor Laegeforen. 1997 Apr 30;117(11):1606-10.
51. Gran JT. The epidemiology of chronic generalized musculoskeletal pain. Best Pract Res Clin Rheumatol. 2003 Aug;17(4):547-61.
52. Fassa AG, Facchini LA, Dall'Agnol MM, Christiani DC. Child labor and musculoskeletal disorders: the Pelotas (Brazil) epidemiological survey. Public Health Rep. 2005 Nov-Dec;120(6):665-73.
53. Rethelyi JM, Berghammer R, Ittzes A, Szumska I, Purebl G, Csoboth C. Comorbidity of pain problems and depressive symptoms in young women: results from a cross-sectional survey among women aged 15-24 in Hungary. Eur J Pain. 2004 Feb;8(1):63-9.
54. Andersson HI. The epidemiology of chronic pain in a Swedish rural area. Qual Life Res. 1994 Dec;3 Suppl 1:S19-26.
55. Leveille SG, Ling S, Hochberg MC, Resnick HE, Bandeen-Roche KJ, Won A, et al. Widespread musculoskeletal pain and the progression of disability in older disabled women. Ann Intern Med. 2001 Dec 18;135(12):1038-46.
56. Arvidsson S, Arvidsson B, Fridlund B, Bergman S. Health predicting factors in a general population over an eight-year period in subjects with and without chronic musculoskeletal pain. Health Qual Life Outcomes. 2008;6:98. doi: 10.1186/1477-7525-6-98
57. Woo J, Leung J, Lau E. Prevalence and correlates of musculoskeletal pain in Chinese elderly and the impact on 4-year physical function and quality of life. Public Health. 2009 Aug;123(8):549-56.
58. Blyth FM, March LM, Nicholas MK, Cousins MJ. Chronic pain, work performance and litigation. Pain. 2003 May;103(1-2):41-7.
59. Hagen KB, Thune O. Work incapacity from low back pain in the general population. Spine (Phila Pa 1976). 1998 Oct 1;23(19):2091-5.
60. Australian Institute of Health and Welfare. Health system expenditure on disease and injury in Australia, 2004–05 [Internet]. Canberra: AIHW; 2010 [cited 2017 17 Jan]; AIHW Cat. no. HSE 87. Available from: http://www.aihw.gov.au/publication-detail/?id=6442468349
61. Straus BN. Chronic pain of spinal origin: the costs of intervention. Spine. 2002 Nov 15;27(22):2614-9; discussion 2620.
62. Baldwin ML. Reducing the costs of work-related musculoskeletal disorders: targeting strategies to chronic disability cases. J Electromyogr Kinesiol. 2004 Feb;14(1):33-41. doi: 10.1016/j.jelekin.2003.09.013
63. Coyte PC, Asche CV, Croxford R, Chan B. The economic cost of musculoskeletal disorders in Canada. Arthritis Care Res. 1998 Oct;11(5):315-25.
64. . MIMS. APO-Paracetamol. Available from: https://www-mimsonline-com-au.ezproxy.lib.rmit.edu.au/Search/AbbrPI.aspx?ModuleName=Product%20Info&searchKeyword=acetaminophen&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=83670001_2
65. Serpell M. Pharmacotherapy of pain. In: Handbook of Pain Management. London: Springer Healthcare Ltd.: Tarporley; 2008 p.49-72.
66. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev. 2006 (1):CD004257. doi: 10.1002/14651858.CD004257.pub2
67. Machado GC, Maher CG, Ferreira PH, Pinheiro MB, Lin CW, Day RO, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015 Mar 31;350:h1225. doi: 10.1136/bmj.h1225
68. Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. Arch Intern Med. 2007 Feb 26;167(4):394-9. doi: 10.1001/archinte.167.4.394
69. AIHW. Hospital separations due to injury and poisoning, Australia 2009-10 [Internet]. Canberra: AIHW; 2012 [cited 2017 17 Jan]; AIHW Cat. no. INJCAT 145. Available from: http://www.aihw.gov.au/publication-detail/?id=60129542183
70. Katzung BG, Masters SB, Trevor AJ. Basic & clinical pharmacology. 11th ed. ed. New York : London: McGraw-Hill Medical
McGraw-Hill distributor; 2009.
71. Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2005 May;64(5):669-81. doi: 10.1136/ard.2004.028886
72. Biswal S, Medhi B, Pandhi P. Longterm efficacy of topical nonsteroidal antiinflammatory drugs in knee osteoarthritis: metaanalysis of randomized placebo controlled clinical trials. J Rheumatol. 2006 Sep;33(9):1841-4.
73. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Nonsteroidal anti-inflammatory drugs for low back pain: an updated Cochrane review. Spine (Phila Pa 1976). 2008 Jul 15;33(16):1766-74. doi: 10.1097/BRS.0b013e31817e69d3
74. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev. 2012;1:CD008921. doi: 10.1002/14651858.CD008921.pub2

75. Brown DC. Adrenal corticosteroids, antagonists, corticotrophin. In: Bennett PN, Brown MJ, editors. Clinical Pharmacology. 9th edition ed: Elsevier Health Sciences UK; 2003 p.663-678.
76. Schumacher MA, Basbaum AI, Way WL. Opioid Analgesics & Antagonists. In: Katzung BG, Masters SB, Trevor AJ, editors. Basic and clinical pharmacology. 12th ed. New York : London: McGraw-Hill Medical; 2012 p.543-564.
77. Grewal J. Pain and analgesics. In: Bennett PN, Brown MJ, editors. Clinical Pharmacology. 9th edition ed: Elsevier Health Sciences UK; 2003 p.319-344.
78. Crofford LJ. Adverse effects of chronic opioid therapy for chronic musculoskeletal pain. Nat Rev Rheumatol. 2010 Apr;6(4):191-7. doi: 10.1038/nrrheum.2010.24
79. Baldini A, Von Korff M, Lin EH. A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide. Prim Care Companion CNS Disord. 2012;14(3):PCC.11m01326. doi: 10.4088/PCC.11m01326
80. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain. 2004 Dec;112(3):372-80. doi: 10.1016/j.pain.2004.09.019
81. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015 Feb 17;162(4):276-86. doi: 10.7326/M14-2559
82. Jensen MK, Thomsen AB, Hojsted J. 10-year follow-up of chronic non-malignant pain patients: opioid use, health related quality of life and health care utilization. Eur J Pain. 2006 Jul;10(5):423-33. doi: 10.1016/j.ejpain.2005.06.001
83. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. J Bone Joint Surg Am. 2009 Apr;91(4):919-27. doi: 10.2106/JBJS.H.00286
84. Leo RJ, Quinton WJ, Ebert MH. Psychological and Psychosocial Evaluation of the Chronic Pain Patient. In: Vadivelu N, Urman RD, Hines RL, editors. Essentials of Pain Management: Springer New York; 2011 p.203-36.
85. Verdugo RJ, Salinas RA, Castillo JL, Cea JG. Surgical versus non-surgical treatment for carpal tunnel syndrome. Cochrane Database Syst Rev. 2008 (4):CD001552. doi: 10.1002/14651858.CD001552.pub2
86. Drazin D, Shirzadi A, Jeswani S, Ching H, Rosner J, Rasouli A, et al. Direct surgical repair of spondylolysis in athletes: indications, techniques, and outcomes. Neurosurg Focus. 2011 Nov;31(5):E9. doi: 10.3171/2011.9.FOCUS11180
87. Jacobs WC, Arts MP, van Tulder MW, Rubinstein SM, van Middelkoop M, Ostelo RW, et al. Surgical techniques for sciatica due to herniated disc, a systematic review. Eur Spine J. 2012 Jul 20:2232-51. doi: 10.1007/s00586-012-2422-9
88. Manchikanti L, Derby R, Benyamin RM, Helm S, Hirsch JA. A systematic review of mechanical lumbar disc decompression with nucleoplasty. Pain Physician. 2009 May-Jun;12(3):561-72.
89. Tamaoki MJ, Belloti JC, Lenza M, Matsumoto MH, Gomes Dos Santos JB, Faloppa F. Surgical versus conservative interventions for treating acromioclavicular dislocation of the shoulder in adults. Cochrane Database Syst Rev. 2010 (8):CD007429. doi: 10.1002/14651858.CD007429.pub2
90. Coghlan JA, Buchbinder R, Green S, Johnston RV, Bell SN. Surgery for rotator cuff disease. Cochrane Database Syst Rev. 2008 (1):CD005619. doi: 10.1002/14651858.CD005619.pub2
91. Trinh K, Graham N, Irnich D, Cameron ID, Forget M. Acupuncture for neck disorders. Cochrane Database Syst Rev. 2016 (5):CD004870. doi: 10.1002/14651858.CD004870.pub4
92. Furlan AD, van Tulder M, Cherkin D, Tsukayama H, Lao L, Koes B, et al. Acupuncture and dry-needling for low back pain: an updated systematic review within the framework of the cochrane collaboration. Spine. 2005 Apr 15;30(8):944-63.
93. Lee TL, Zheng Z. Acupuncture Pain Research: Quantitative and Qualitative. In: Lin YC, Hsu ESZ, editors. Acupuncture for pain management. Heidelberg: Springer; 2014 p.117-137.
94. Manheimer E, Cheng K, Linde K, Lao L, Yoo J, Wieland S, et al. Acupuncture for peripheral joint osteoarthritis. Cochrane Database Syst Rev. 2010 (1):CD001977. doi: 10.1002/14651858.CD001977.pub2
95. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. ed. Hillsdale, N.J: L. Erlbaum Associates; 1988.
96. Macpherson H, Scullion A, Thomas KJ, Walters S. Patient reports of adverse events associated with acupuncture treatment: a prospective national survey. Qual Saf Health Care. 2004 Oct;13(5):349-55. doi: 10.1136/qhc.13.5.349
97. Maund E, Craig D, Suekarran S, Neilson A, Wright K, Brealey S, et al. Management of frozen shoulder: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2012;16(11):1-264. doi: 10.3310/hta16110
98. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis. 2005 Apr;64(4):544-8. doi: 10.1136/ard.2004.028746
99. Gross A, Miller J, D'Sylva J, Burnie SJ, Goldsmith CH, Graham N, et al. Manipulation or mobilisation for neck pain. Cochrane Database Syst Rev. 2010 (1):CD004249. doi: 10.1002/14651858.CD004249.pub3
100. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. Cochrane

Database Syst Rev. 2008 (1):CD002822. doi: 10.1002/14651858.CD002822.pub3
101. Collins NJ, Bisset LM, Crossley KM, Vicenzino B. Efficacy of nonsurgical interventions for anterior knee pain: systematic review and meta-analysis of randomized trials. Sports Med. 2012 Jan 1;42(1):31-49. doi: 10.2165/11594460-000000000-00000
102. Buszewicz M, Rait G, Griffin M, Nazareth I, Patel A, Atkinson A, et al. Self management of arthritis in primary care: randomised controlled trial. BMJ. 2006 Oct 28;333(7574):879. doi: 10.1136/bmj.38965.375718.80
103. Engers A, Jellema P, Wensing M, van der Windt DA, Grol R, van Tulder MW. Individual patient education for low back pain. Cochrane Database Syst Rev. 2008 (1):CD004057. doi: 10.1002/14651858.CD004057.pub3
104. Eccleston C, Williams AC, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2009 (2):CD007407. doi: 10.1002/14651858.CD007407.pub2
105. Vasudevan S. Creating a Multidisciplinary Team. In: Multidisciplinary Management of Chronic Pain: A Practical Guide for Clinicians. Cham: Springer International Publishing; 2015 p.133-153.
106. Trevor AJ, Way WL. Sedative-Hypnotic Drugs. In: Katzung BG, Masters SB, Trevor AJ, editors. Basic and clinical pharmacology. 12th ed. New York : London: McGraw-Hill Company; 2009 p.373-388.
107. Lang E, Liebig K, Kastner S, Neundorfer B, Heuschmann P. Multidisciplinary rehabilitation versus usual care for chronic low back pain in the community: effects on quality of life. Spine J. 2003 Jul-Aug;3(4):270-6.
108. Chipchase L, Sheffield D, Hill P. The long-term effectiveness of pain management programs: A systematic review and meta-analysis. J Pain Manage. 2012;5(3):215-230.
109. Flor H, Fydrich T, Turk DC. Efficacy of multidisciplinary pain treatment centers: a meta-analytic review. Pain. 1992 May;49(2):221-30.
110. Tong B, Stevenson C. Comorbidity of cardiovascular disease, diabetes and chronic kidney disease in Australia [Internet]. Canberra: AIHW; 2007 [cited 2017 17 Jan]; AIHW Cat. no. CVD 37. Available from: http://www.aihw.gov.au/publication-detail/?id=6442468009
111. Angold A, Costello EJ, Erkanli A. Comorbidity. J Child Psychol Psychiatry. 1999 Jan;40(1):57-87.
112. Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. J Clin Epidemiol. 2001 Jul;54(7):661-74.
113. Australian Institute of Health and Welfare. National comorbidity initiative: A review of data collections relating to people with coexisting substance use and mental health disorders [Internet]. Canberra: AIHW; 2005 [cited 2017 17 Jan]; AIHW Cat. no. PHE 60. Available from: http://www.aihw.gov.au/publication-detail/?id=6442467722
114. Teesson M, Proudfoot H. Comorbid mental disorders and substance use disorders: epidemiology, prevention and treatment.2003: Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/D588E61C48428185CA256F1900044A02/$File/mono_comorbid.pdf.
115. Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. Arch Gen Psychiatry. 1998 Nov;55(11):967-72.
116. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994 Jan;51(1):8-19.
117. Kessler RC. The National Comorbidity Survey of the United States. International Review of Psychiatry. 1994;6:365-76.
118. Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression. A causal analysis. Arch Gen Psychiatry. 1993 Jan;50(1):36-43.
119. Tunks ER, Crook J, Weir R. Epidemiology of chronic pain with psychological comorbidity: prevalence, risk, course, and prognosis. Can J Psychiatry. 2008 Apr;53(4):224-34.
120. Scher AI, Stewart WF, Lipton RB. The comorbidity of headache with other pain syndromes. Headache. 2006 Oct;46(9):1416-23. doi: 10.1111/j.1526-4610.2006.00584.x
121. Wilson A, Yu HT, Goodnough LT, Nissenson AR. Prevalence and outcomes of anemia in rheumatoid arthritis: a systematic review of the literature. Am J Med. 2004 Apr 5;116 Suppl 7A:50S-57S. doi: 10.1016/j.amjmed.2003.12.012
122. Buskila D, Cohen H. Comorbidity of fibromyalgia and psychiatric disorders. Curr Pain Headache Rep. 2007 Oct;11(5):333-8.
123. Ursini F, Naty S, Grembiale RD. Fibromyalgia and obesity: the hidden link. Rheumatol Int. 2011 Nov;31(11):1403-8. doi: 10.1007/s00296-011-1885-z
124. Nicholson B, Verma S. Comorbidities in chronic neuropathic pain. Pain Med. 2004 Mar;5 Suppl 1:S9-S27.
125. Ohayon MM, Stingl JC. Prevalence and comorbidity of chronic pain in the German general population. J Psychiatr Res. 2012 Apr;46(4):444-50. doi: 10.1016/j.jpsychires.2012.01.001
126. McCarberg B. Managing the comorbidities of postherpetic neuralgia. J Am Acad Nurse Pract. 2003

Dec;15(12 Suppl):16-21; quiz 22-4.
127. Giamberardino MA, Affaitati G, Martelletti P, Tana C, Negro A, Lapenna D, et al. Impact of migraine on fibromyalgia symptoms. J Headache Pain. 2015 Dec;17(1):28. doi: 10.1186/s10194-016-0619-8
128. Radner H, Smolen JS, Aletaha D. Impact of comorbidity on physical function in patients with rheumatoid arthritis. Ann Rheum Dis. 2010 Mar;69(3):536-41. doi: 10.1136/ard.2009.118430
129. Wang XH, Luo YK, Liang SM. Fundamental of Traditional Chinese Medicine [中医学基础]. 1st ed. Shanghai: Shanghai Science and Technology Press; 1995.
130. Wang XH. Chinese medicine fundamental theory [中医基础理论]. 1st ed. Beijing: People's Medical Publishing House Co., LTD [人民卫生出版社]; 2001.
131. Shaonghai Institute of Chinese medicine. Tuina [推拿学]. 1st ed. Shanghai: Shanghai People's Publishing House [上海人民出版社]; 1975.
132. Wang YY. Chinese medicine internal medicine [中医内科学]. 1st ed. Beijing: People's Medical Publishing House [人民卫生出版社]; 1999.
133. Yin HH. Theory of Chinese Medicine (in Simplified Chinese) [中医基础理论]. 1st ed: Shanghai Science Technology Press (上海科学技术出版社); 1984.
134. Zhang BY, Dong JH, Zhou ZY. Chinese medicine internal medicine [中医内科学]. Shanghai Science Technology Press; 1985.
135. Xue C, Liu XJ. Lower back pain (LBP). In: Lecture notes for KP610/COTH1040: Acupuncture practice 1 (Techniques and treatment). Bundoora: RMIT University; 2002 p.179-80.
136. Yang CS, He SH, Liu GJ, Chen hP, Zhang JW. Acupuncture treatment [针灸治疗学]. 1st ed. Shanghai: Shanghai Science Technology Press (上海科学技术出版社); 1985.
137. Shi X. Acupuncture and moxibustion therapy [针灸治疗学]. 1st ed: People's Medical Publishing House Co., LTD; 2001.
138. Essentials of Chinese acupuncture. First edition. ed. Beijing: Foreign Languages Press; 1980.
139. Norris CMa. Back and trunk treamtent protocols. In: Acupuncture : treatment of musculoskeletal conditions. Oxford: Butterworth-Heinemann; 2001 p.160-74.
140. Liu L, Liu Z. Lumbago. In: Liu Z, editor. Essentials of Chinese Medicine, Volume 3. Dordrecht: Springer; 2009 p.199-205.
141. Maciocia G. The Practice of Chinese Medicine : the Treatment of Diseases with Acupuncture and Chinese Herbs [In: Lower backache and sciatica. 2008. London
Edinburgh
New York: Elsevier Health Sciences UK.
142. Tian SS. The complete medical book of Feng Zhao Zhang [冯兆张医学全书]. 1st ed: China press of traditional Chinese medicine [中国中医药出版社]; 1999. p. 942.
143. Wang XH. Fundamental theory of Chinese medicine [中医基础理论]. 1st ed. Beijing: People's Medical Publishing House Co., LTD [人民卫生出版社]; 1999.
144. Luo YF. Acupuncture points [腧穴学]. 1st ed: Shanghai Science and Technology Press; 1996.
145. Heller JL. Opiate and opioid withdrawal. 2016 [cited 2016 03/08/2016]. Available from: https://medlineplus.gov/ency/article/000949.htm
146. Yang ZM, Guo EJ, Guo CJ. Electro acupuncture needling technique. In: Chen NM, Yang WH, Liang SZ, editors. Needling technique and moxibustion [刺法灸法学]. Shanghai: Shang Science and Technology Press; 1996 p.68-71.
147. Xi YJ, Si TL. Acupuncture and moxibustion method [针法灸法学]. Shanghai: Shanghai Science and Technology Press; 1985.
148. Yang ZM, Guo EJ, Guo CJ. Application of modern acupuncture and moxibustion. In: Chen NM, Yang WH, Liang SZ, editors. Needling technique and moxibustion [刺法灸法学]. Shanghai: Shang Science and Technology Press; 1996 p.100-136.
149. Wilkinson J, Faleiro R. Acupuncture in pain management. Continuing Education in Anaesthesia, Critical Care & Pain. 2007 August 1, 2007;7(4):135-138. doi: 10.1093/bjaceaccp/mkm021
150. Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. Trends Neurosci. 2003 Jan;26(1):17-22.
151. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965 Nov 19;150(3699):971-9.
152. Lee AD, Hsu ESZ. Mechanisms of Acupuncture Analgesia. In: Lin Y-C, Hsu ES-Z, editors. Acupuncture for pain management. Heidelberg: Springer; 2014 p.73-85.
153. McEwen BS, Kalia M. The role of corticosteroids and stress in chronic pain conditions. Metabolism. 2010 Oct;59 Suppl 1:S9-15. doi: 10.1016/j.metabol.2010.07.012
154. Baldry PE. Acupuncture, Trigger Points and Musculoskeletal Pain (Third Edition). Churchill Livingstone; 2005.
155. Taylor AM, Becker S, Schweinhardt P, Cahill C. Mesolimbic dopamine signaling in acute and chronic

pain: implications for motivation, analgesia, and addiction. Pain. 2016 Jun;157(6):1194-8. doi: 10.1097/j.pain.0000000000000494
156. Yang CH, Lee BH, Sohn SH. A possible mechanism underlying the effectiveness of acupuncture in the treatment of drug addiction. Evid Based Complement Alternat Med. 2008 Sep;5(3):257-66. doi: 10.1093/ecam/nem081
157. Wiseman N, Ye F. A Practical Dictionary Of Chinese Medicine. 2nd ed. Beijing: People's Medical and Publishing House; 2002.
158. British Acupuncture Council. Ask an expert - about acupuncture - How often? [cited 2016 05/09/2016]. Available from: http://www.acupuncture.org.uk/category/public-content/public-ask-an-expert/ask-an-expert-about-acupuncture/ask-an-expert-about-acupuncture-how-often.html
159. Yuan J, Kerr D, Park J, Liu XH, McDonough S. Treatment regimens of acupuncture for low back pain--a systematic review. Complement Ther Med. 2008 Oct;16(5):295-304.
160. Liu L, Skinner M, McDonough S, Mabire L, Baxter GD. Acupuncture for low back pain: an overview of systematic reviews. Evid Based Complement Alternat Med. 2015;2015:328196. doi: 10.1155/2015/328196
161. Zhu LB, Chan WC, Lo KC, Yum TP, Li L. Wrist-ankle acupuncture for the treatment of pain symptoms: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2014;2014:261709. doi: 10.1155/2014/261709
162. Yang B, Yi G, Hong W, Bo C, Wang Z, Liu Y, et al. Efficacy of acupuncture on fibromyalgia syndrome: a meta-analysis. J Tradit Chin Med. 2014 Aug;34(4):381-91.
163. Langevin HM, Schnyer R, MacPherson H, Davis R, Harris RE, Napadow V, et al. Manual and electrical needle stimulation in acupuncture research: pitfalls and challenges of heterogeneity. J Altern Complement Med. 2015 Mar;21(3):113-28. doi: 10.1089/acm.2014.0186
164. Linde K, Streng A, Jurgens S, Hoppe A, Brinkhaus B, Witt C, et al. Acupuncture for patients with migraine: a randomized controlled trial. JAMA. 2005 May 4;293(17):2118-25. doi: 10.1001/jama.293.17.2118
165. Schnyer RN, Conboy LA, Jacobson E, McKnight P, Goddard T, Moscatelli F, et al. Development of a Chinese medicine assessment measure: an interdisciplinary approach using the delphi method. J Altern Complement Med. 2005 Dec;11(6):1005-13.
166. Lee S, Tsang A, Huang YQ, Zhang MY, Liu ZR, He YL, et al. Arthritis and physical-mental comorbidity in metropolitan China. Journal of Psychosomatic Research. 2007 Jul;63(1):1-7. Available from: PsycINFO.
167. Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, et al. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. Pain. 2005 Feb;113(3):331-9.
168. Ijzelenberg W, Burdorf A. Impact of musculoskeletal co-morbidity of neck and upper extremities on healthcare utilisation and sickness absence for low back pain. Occupational and Environmental Medicine. 2004;61(10):806-810. doi: 10.1136/oem.2003.011635
169. Kirkness CS, Yu J, Asche CV. The effect on comorbidity and pain in patients with osteoarthritis. J Pain Palliat Care Pharmacother. 2008;22(4):336-48. doi: 10.1080/15360280802536649
170. Anderson G. Chronic Care: Making the Case for Ongoing Care2010 [cited 2014: Available from: http://www.rwjf.org/content/dam/farm/reports/reports/2010/rwjf54583.
171. Caporali R, Cimmino MA, Sarzi-Puttini P, Scarpa R, Parazzini F, Zaninelli A, et al. Comorbid conditions in the AMICA study patients: effects on the quality of life and drug prescriptions by general practitioners and specialists. Semin Arthritis Rheum. 2005 Aug;35(1 Suppl 1):31-7. doi: 10.1016/j.semarthrit.2005.02.004
172. Reeves BC, Deeks JJ, Higgins JP, Wells GA. 13.5.2.3 Tools for assessing methodological quality or risk of bias in non-randomized studies. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. 5.1.0 ed: The Cochrane Collaboration; 2011 p.417-8.[cited 20/06/2015].
173. Bruning AH, Heller HM, Kieviet N, Bakker PC, de Groot CJ, Dolman KM, et al. Antidepressants during pregnancy and postpartum hemorrhage: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2015 Jun;189:38-47. doi: 10.1016/j.ejogrb.2015.03.022
174. Asmundson GJ, Jacobson SJ, Allerdings MD, Norton GR. Social phobia in disabled workers with chronic musculoskeletal pain. Behav Res Ther. 1996 Nov-Dec;34(11-12):939-43.
175. Atkinson JH, Slater MA, Patterson TL, Grant I, Garfin SR. Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: a controlled study. Pain. 1991 May;45(2):111-21. doi: 10.1016/0304-3959(91)90175-W
176. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain. 2003 Nov;106(1-2):127-33.
177. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. Pain. 2004 Sep;111(1-2):77-83. doi: 10.1016/j.pain.2004.06.002
178. Polatin PB, Kinney RK, Gatchel RJ, Lillo E, Mayer TG. Psychiatric illness and chronic low-back pain. The mind and the spine--which goes first? Spine (Phila Pa 1976). 1993 Jan;18(1):66-71.
179. Stupar M, Cote P, French MR, Hawker GA. The association between low back pain and osteoarthritis of the hip and knee: a population-based cohort study. J Manipulative Physiol Ther. 2010 Jun;33(5):349-54.

180. Nilsdotter AK, Petersson IF, Roos EM, Lohmander LS. Predictors of patient relevant outcome after total hip replacement for osteoarthritis: a prospective study. Ann Rheum Dis. 2003 Oct;62(10):923-30.
181. Bischoff-Ferrari HA, Lingard EA, Losina E, Baron JA, Roos EM, Phillips CB, et al. Psychosocial and geriatric correlates of functional status after total hip replacement. Arthritis Rheum. 2004 Oct 15;51(5):829-35. doi: 10.1002/art.20691
182. Tikiz C, Muezzinoglu T, Pirildar T, Taskn EO, Frat A, Tuzun C. Sexual dysfunction in female subjects with fibromyalgia. J Urol. 2005 Aug;174(2):620-3.
183. Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosomatic medicine. 2008;70(8):890-7.
184. Bernatsky S, Dobkin PL, De Civita M, Penrod JR. Comorbidity and physician use in fibromyalgia. Swiss Medical Weekly. 2005;135(5-6):76-81.
185. Black SA, Goodwin JS, Markides KS. The association between chronic diseases and depressive symptomatology in older Mexican Americans. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 1998;53(3):M188-94.
186. Braden JB, Sullivan MD. Suicidal Thoughts and Behavior Among Adults With Self-Reported Pain Conditions in the National Comorbidity Survey Replication. Journal of Pain. 2008;9(12):1106-1115. doi: 10.1016/j.jpain.2008.06.004
187. Buist-Bouwman MA, De Graaf R, Vollebergh WAM, Ormel J. Comorbidity of physical and mental disorders and the effect on work-loss days. Acta Psychiatrica Scandinavica. 2005;111(6):436-443. doi: 10.1111/j.1600-0447.2005.00513.x
188. Cakit BD, Taskin S, Nacir B, Unlu I, Genc H, Erdem HR. Comorbidity of fibromyalgia and cervical myofascial pain syndrome. Clin Rheumatol. 2010 Apr;29(4):405-11. doi: 10.1007/s10067-009-1342-5
189. Ciapparelli A, Bazzichi L, Consoli G, Marazziti D, Dell'Osso MC, Del Debbio A, et al. The impact of psychiatric comorbidity on health-related quality of life in women with fibromyalgia. Clinical Neuropsychiatry. 2008;5(5):217-224.
190. Fernandez-de-Las-Penas C, Hernandez-Barrera V, Carrasco-Garrido P, Alonso-Blanco C, Palacios-Cena D, Jimenez-Sanchez S, et al. Population-based study of migraine in Spanish adults: relation to socio-demographic factors, lifestyle and co-morbidity with other conditions. J Headache Pain. 2010 Apr;11(2):97-104. doi: 10.1007/s10194-009-0176-5
191. Gili M, Comas A, Garcia-Garcia M, Monzon S, Antoni SB, Roca M. Comorbidity between common mental disorders and chronic somatic diseases in primary care patients. Gen Hosp Psychiatry. 2010 May-Jun;32(3):240-5. doi: 10.1016/j.genhosppsych.2010.01.013
192. Gureje O, Akinpelu AO, Uwakwe R, Udofia O, Wakil A. Comorbidity and impact of chronic spinal pain in Nigeria. Spine. 2007;32(17):E495-500. doi: 10.1097/BRS.0b013e31810768fc
193. Hägg O, Fritzell P, Nordwall A, And the Swedish Lumbar Spine Study G. Characteristics of patients with chronic low back pain selected for surgery: a comparison with the general population reported from the Swedish lumbar spine study. Spine. 2002;27(11):1223-31.
194. Kauppila AM, Kyllonen E, Mikkonen P, Ohtonen P, Laine V, Siira P, et al. Disability in end-stage knee osteoarthritis. Disability and rehabilitation. 2009;31(5):370-80.
195. Korszun A, Hinderstein B, Wong M. Comorbidity of depression with chronic facial pain and temporomandibular disorders. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 1996;82(5):496-500.
196. Kurtze N, Svebak S. Fatigue and patterns of pain in fibromyalgia: Correlations with anxiety, depression and co-morbidity in a female county sample. British Journal of Medical Psychology. 2001;74(4):523-537. doi: 10.1348/000711201161163
197. Linder J, Ekholm KS, Jansen GB, Lundh G, Ekholm J. Long-term sick leavers with difficulty in resuming work: Comparisons between psychiatric-somatic comorbidity and monodiagnosis. International Journal of Rehabilitation Research. 2009;32(1):20-35. doi: 10.1097/MRR.0b013e328306351d
198. Mäkelä M, Heliövaara M, Sainio P, Knekt P, Impivaara O, Aromaa A. Shoulder joint impairment among Finns aged 30 years or over: Prevalence, risk factors and co-morbidity. Rheumatology. 1999;38(7):656-662. doi: 10.1093/rheumatology/38.7.656
199. Malmgren Olsson EB, Bergdahl J. Temperament and character personality dimensions in patients with nonspecific musculoskeletal disorders. The Clinical journal of pain. 2006;22(7):625-31.
200. Mangani I, Cesari M, Kritchevsky SB, Maraldi C, Carter CS, Atkinson HH, et al. Physical exercise and comorbidity. Results from the Fitness and Arthritis in Seniors Trial (FAST). Aging clinical and experimental research. 2006;18(5):374-80.
201. Raphael KG, Janal MN, Nayak S. Comorbidity of fibromyalgia and posttraumatic stress disorder symptoms in a community sample of women. Pain Medicine. 2004;5(1):33-41. doi: 10.1111/j.1526-4637.2004.04003.x
202. Sareen J, Cox BJ, Clara I, Asmundson GJG. The relationship between anxiety disorders and physical disorders in the U.S. National Comorbidity Survey. Depression and Anxiety. 2005;21(4):193-202. doi:

10.1002/da.20072
203. Schur EA, Afari N, Furberg H, Olarte M, Goldberg J, Sullivan PF, et al. Feeling bad in more ways than one: Comorbidity patterns of medically unexplained and psychiatric conditions. Journal of General Internal Medicine. 2007;22(6):818-821. doi: 10.1007/s11606-007-0140-5
204. Sipilä K, Ylöstalo PV, Joukamaa M, Knuuttila ML. Comorbidity between facial pain, widespread pain, and depressive symptoms in young adults. Journal of Orofacial Pain. 2006;20(1):24-30.
205. Tashjian RZ, Henn RF, Kang L, Green A. The effect of comorbidity on self-assessed function in patients with a chronic rotator cuff tear. J Bone Joint Surg Am. 2004 Feb;86-A(2):355-62.
206. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. Journal of Pain. 2008 10;9(10):883-891.
207. van Dijk GM, Veenhof C, Lankhorst GJ, Dekker J. Limitations in activities in patients with osteoarthritis of the hip or knee: the relationship with body functions, comorbidity and cognitive functioning. Disabil Rehabil. 2009;31(20):1685-91. doi: 10.1080/09638280902736809
208. Verri AP, Proietti Cecchini A, Galli C, Granella F, Sandrini G, Nappi G. Psychiatric comorbidity in chronic daily headache. Cephalalgia, Supplement. 1998;18(SUPPL. 21):45-49.
209. Whitson HE, Sanders LL, Pieper CF, Morey MC, Oddone EZ, Gold DT, et al. Correlation between symptoms and function in older adults with comorbidity. Journal of the American Geriatrics Society. 2009;57(4):676-682. doi: 10.1111/j.1532-5415.2009.02178.x
210. Wolfe F, Michaud K. Predicting depression in rheumatoid arthritis: The signal importance of pain extent and fatigue, and comorbidity. Arthritis Care and Research. 2009;61(5):667-673. doi: 10.1002/art.24428
211. Wolf JM, Green A. Influence of comorbidity on self-assessment instrument scores of patients with idiopathic adhesive capsulitis. J Bone Joint Surg Am. 2002 Jul;84-A(7):1167-73.
212. Williams Russo P, Urquhart BL, Sharrock NE, Charlson ME. Post-operative delirium: predictors and prognosis in elderly orthopedic patients. Journal of the American Geriatrics Society. 1992;40(8):759-67.
213. Tamber AL, Bruusgaard D. Self-reported faintness or dizziness -- comorbidity and use of medicines. An epidemiological study. Scand J Public Health. 2009 Aug;37(6):613-20.
214. Aguglia A, Salvi V, Maina G, Rossetto I, Aguglia E. Fibromyalgia syndrome and depressive symptoms: Comorbidity and clinical correlates. Journal of Affective Disorders. 2011;128(3):262-266. Available from: PsycINFO. doi: 10.1016/j.jad.2010.07.004
215. Aristeguieta LMR, Ortiz GPS, Ballesteros LE, González AL, Muñoz G. Treatment and follow-up of referred otic symptomatology in 23 patients with diagnosed temporomandibular disorders. Audiological Medicine. 2006;4(2):73-81. Available from: PsycINFO. doi: 10.1080/16513860600836715
216. Arnold LM, Palmer RH, Gendreau RM, Chen W. Relationships among pain, depressed mood, and global status in fibromyalgia patients: post hoc analyses of a randomized, placebo-controlled trial of milnacipran. Psychosomatics [Clinical Trial, Phase III; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2012;53(4):371-9. doi: 10.1016/j.psym.2012.02.005
217. Blackman JA, Gurka MJ, Gurka KK, Oliver MN. Emotional, developmental and behavioural co‐morbidities of children with chronic health conditions. Journal of Paediatrics and Child Health. 2011;47(10):742-747. Available from: PsycINFO. doi: 10.1111/j.1440-1754.2011.02044.x
218. Carbonell-Baeza A, Ruiz JR, Aparicio VA, Ortega FB, Delgado-Fernández M. The 6-Minute Walk Test in Female Fibromyalgia Patients: Relationship With Tenderness, Symptomatology, Quality of Life, and Coping Strategies. Pain Management Nursing. 2013;14(4):193-9. doi: 10.1016/j.pmn.2011.01.002
219. Fitzgerald GK, Piva SR, Gil AB, Wisniewski SR, Oddis CV, Irrgang JJ. Agility and perturbation training techniques in exercise therapy for reducing pain and improving function in people with knee osteoarthritis: a randomized clinical trial. Physical therapy [Randomized Controlled Trial; Research Support, N.I.H., Extramural]. 2011;91(4):452-69. doi: 10.2522/ptj.20100188
220. Hoogeboom TJ, Den Broeder AA, Swierstra BA, De Bie RA, Van Den Ende CHM. Joint-pain comorbidity, health status, and medication use in hip and knee osteoarthritis: A cross-sectional study. Arthritis Care and Research. 2012;64(1):54-8. doi: 10.1002/acr.20647
221. Kane S, Conus S, Haltom D, Hirshorn K, Pak Y, Vigdorchik J. A Shoulder Health Survey: Correlating Behaviors and Comorbidities With Shoulder Problems. Sports Health: A Multidisciplinary Approach. 2010;2(2):119-134. doi: 10.1177/1941738109338358
222. Klemenc-Ketiš Z, Kersnik J, Novak-Glavač D. Determinants of depression and anxiety in family practice patients with comorbidities. Die Wiener klinische Wochenschrift (The Middle European Journal of Medicine). 2010;122(Supplement 2):35-39. doi: 10.1007/s00508-010-1337-x
223. Lee J, Dunlop D, Ehrlich-Jones L, Semanik P, Song J, Manheim L, et al. Public health impact of risk factors for physical inactivity in adults with rheumatoid arthritis. Arthritis care & research [Randomized Controlled Trial; Research Support, N.I.H., Extramural]. 2012;64(4):488-93. doi: 10.1002/acr.21582
224. McWilliams LA, Higgins KS. Associations between pain conditions and borderline personality disorder symptoms: findings from the National Comorbidity Survey Replication. Clin J Pain. 2013 Jun;29(6):527-32. doi:

10.1097/AJP.0b013e31826ab5d0
225. Rehm SE, Koroschetz J, Gockel U, Brosz M, Freynhagen R, Tölle TR, et al. A cross-sectional survey of 3035 patients with fibromyalgia: subgroups of patients with typical comorbidities and sensory symptom profiles. Rheumatology. 2010;49(6):1146-1146. doi: 10.1093/rheumatology/keq066
226. Shillam CR, Dupree Jones K, Miller L. Fibromyalgia symptoms, physical function, and comorbidity in middle-aged and older adults. Nurs Res. 2011 Sep-Oct;60(5):309-17. doi: 10.1097/NNR.0b013e31822bbdfa
227. Singh JA, Lewallen DG. Medical Comorbidity is Associated with Persistent Index Hip Pain after Total Hip Arthroplasty. Pain Med. 2013 Jun 6;14(8):1222-9. doi: 10.1111/pme.12153
228. Singh JA, Lewallen DG. Medical and psychological comorbidity predicts poor pain outcomes after total knee arthroplasty. Rheumatology (Oxford). 2013 May;52(5):916-23. doi: 10.1093/rheumatology/kes402
229. Siu YF, Chan S, Wong KM, Wong WS. The comorbidity of chronic pain and sleep disturbances in a community adolescent sample: Prevalence and association with sociodemographic and psychosocial factors. Pain Medicine. 2012;13(10):1292-1303. Available from: PsycINFO. doi: 10.1111/j.1526-4637.2012.01473.x
230. Wesseling J, Welsing PM, Bierma-Zeinstra SM, Dekker J, Gorter KJ, Kloppenburg M, et al. Impact of self-reported comorbidity on physical and mental health status in early symptomatic osteoarthritis: the CHECK (Cohort Hip and Cohort Knee) study. Rheumatology (Oxford). 2013 Jan;52(1):180-8. doi: 10.1093/rheumatology/kes288
231. Dominick CH, Blyth FM, Nicholas MK. Unpacking the burden: Understanding the relationships between chronic pain and comorbidity in the general population. Pain. 2012;153(2):293-304. Available from: PsycINFO. doi: 10.1016/j.pain.2011.09.018
232. McWilliams LA, Bailey SJ. Associations between adult attachment ratings and health conditions: Evidence from the National Comorbidity Survey Replication. Health Psychology. 2010;29(4):446-453. Available from: PsycINFO. doi: 10.1037/a0020061
233. Schofield DJ, Callander EJ, Shrestha RN, Passey ME, Percival R, Kelly SJ. Association between co-morbidities and labour force participation amongst persons with back problems. Pain. 2012;153(10):2068-2072. Available from: PsycINFO. doi: 10.1016/j.pain.2012.06.020
234. Blackman JA, Conaway MR. Developmental, emotional and behavioral co-morbidities across the chronic health condition spectrum. Journal of Pediatric Rehabilitation Medicine. 2013;6(2):63-71.
235. Raab A, Sengler C, Niewerth M, Klotsche J, Horneff G, Zink A, et al. Comorbidity profiles among adult patients with juvenile idiopathic arthritis (JIA): results of a biologic register. Clin Exp Rheumatol. 2013 Apr 2;31(5):796-802.
236. Rat AC, Guillemin F, Osnowycz G, Delagoutte JP, Cuny C, Mainard D, et al. Total hip or knee replacement for osteoarthritis: Mid- and long-term quality of life. Arthritis care & research. 2010;62(1):54-62. doi: 10.1002/acr.20014
237. Ayers DC, Li W, Oatis C, Rosal MC, Franklin PD. Patient-reported outcomes after total knee replacement vary on the basis of preoperative coexisting disease in the lumbar spine and other nonoperatively treated joints: the need for a musculoskeletal comorbidity index. J Bone Joint Surg Am. 2013 Oct 16;95(20):1833-7. doi: 10.2106/jbjs.l.01007
238. Ayoubi N, Chaaya M, Mahfoud Z, Habib RR, Uthman I, Slim ZN. Risk factors for incident symptomatic knee osteoarthritis: A population-based case control study in Lebanon. International journal of rheumatic diseases. 2013;16(2):211-8. doi: 10.1111/1756-185x.12047
239. Baruth M, Wilcox S, Sharpe PA, Schoffman DE, Becofsky K. Baseline predictors of physical activity in a sample of adults with arthritis participating in a self-directed exercise program. Public health. 2014;128(9):834-41. doi: 10.1016/j.puhe.2014.06.018
240. Ligthart L, Visscher CM, van Houtem CM, Geels LM, Vink JM, de Jongh A, et al. Comorbidity among multiple pain symptoms and anxious depression in a Dutch population sample. J Pain. 2014 Sep;15(9):945-55. doi: 10.1016/j.jpain.2014.06.007
241. Bazzichi L, Rossi A, Giacomelli C, Scarpellini P, Conversano C, Sernissi F, et al. The influence of psychiatric comorbidity on sexual satisfaction in fibromyalgia patients. Clin Exp Rheumatol. 2013 Nov-Dec;31(6 Suppl 79):S81-5.
242. Ismail F, Eisenburger M, Lange K, Schneller T, Schwabe L, Strempel J, et al. Identification of psychological comorbidity in TMD-patients. Cranio. 2015 Apr 2:2151090315Y0000000008. doi: 10.1179/2151090315y.0000000008
243. Migraine and primary headaches: epidemiology, associations, and comorbidity. Headache: The Journal of Head & Face Pain. 2003 11;43(10):1122-1122.
244. Abstracts and citations migraine: clinical features, epidemiology, and comorbidity. Headache: The Journal of Head & Face Pain. 2004 02;44(2):197-198.
245. Migraine comorbidity and epidemiology. Headache: The Journal of Head & Face Pain. 2004 05;44(5):448-449.
246. Migraine, chronic daily headache, and primary headache: clinical characteristics, epidemiology, and comorbidity. Headache: The Journal of Head & Face Pain. 2004 06;44(6):628-632.
247. Anglade JP. Adenosine phosphate of heptaminol and the premenstrual syndrome. Revue Francaise de

Gynecologie et D'Obstetrique. 1985;80(4):245-247.
248. Armstrong AJ, Garrett Mayer E, Ou Yang YC, Carducci MA, Tannock I, de Wit R, et al. Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(25):3965-70.
249. Ashina S, Bendtsen L, Ashina M, Magerl W, Jensen R. Generalized hyperalgesia in patients with chronic tension-type headache. Cephalalgia : an international journal of headache. 2006;26(8):940-8.
250. Baldoni F, Baldaro B, Trombini G. Psychotherapeutic perspectives in urethral syndrome. Stress Medicine. 1995;11(2):79-84.
251. Barahona Rondon L, Maguina Vargas C, Naquira Velarde C, Terashima IA, Tello R. [Human blastocystosis: prospective study symptomatology and associated epidemiological factors]. Rev Gastroenterol Peru. 2003 Jan-Mar;23(1):29-35.
252. Barbier JP, Haccoun P, Bergmann JF, Arnould B, Hamelin B. [Prognostic factors influencing healing of reflux esophagitis. A controlled trial of omeprazole versus ranitidine. Study group Omega]. Annales de gastroentérologie et d'hépatologie. 1993;29(4):213-8.
253. Bigal ME, Gironda M, Tepper SJ, Feleppa M, Rapoport AM, Sheftell FD, et al. Headache prevention outcome and body mass index. Cephalalgia : an international journal of headache. 2006;26(4):445-50.
254. Bock BC, Becker BM, Niaura RS, Partridge R, Fava JL, Trask P. Smoking cessation among patients in an emergency chest pain observation unit: outcomes of the Chest Pain Smoking Study (CPSS). Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2008;10(10):1523-31.
255. Brevetti G, Oliva G, Silvestro A, Scopacasa F, Chiariello M. Prevalence, risk factors and cardiovascular comorbidity of symptomatic peripheral arterial disease in Italy. Atherosclerosis. 2004;175(1):131-138. doi: 10.1016/j.atherosclerosis.2004.03.009
256. Caballero Plasencia AM, Sofos Kontoyannis S, Valenzuela Barranco M, Martin Ruiz JL, Casado Caballero FJ, Lopez Manas JG. Irritable bowel syndrome in patients with dyspepsia: a community based study in southern Europe. European Journal of Gastroenterology and Hepatology. 1999;11:517-22.
257. Calbo F, Dal Re R, Diez Delgado J, On~a S, Sanchez Prados F, Garcia Corbeira P, et al. Comparative trial to assess the reactogenicity of the diphtheria-tetanusacellular pertussis (DTPa) vaccine plus Haemophilus influenza type b (Hib) conjugate vaccine and that of the diphtheria-tetanus-whole cell pertussis (DTPw) vaccine plus Hib conjugate vaccine, administered in single injection as a booster dose to 14-20 months-old children. Medicina Clinica. 2002;118(1):1-4.
258. Chen L, Tao SF, Xu Y, Fang F, Peng SY. Patients' quality of life after laparoscopic or open cholecystectomy. Journal of Zhejiang University. Science. B. 2005;6(7):678-81.
259. Costanza CD, Longstreth GF, Liu AL. Chronic abdominal wall pain: clinical features, health care costs, and long-term outcome (Brief record). Clinical Gastroenterology and Hepatology. 2004;2(5):395-399.
260. de Artaza Varasa T, Valle Muñoz J, Pérez Grueso MJ, García Vela A, Martín Escobedo R, Rodríguez Merlo R, et al. [Effect of Helicobacter pylori eradication on patients with functional dyspepsia]. Revista española de enfermedades digestivas : organo oficial de la Sociedad Española de Patología Digestiva. 2008;100(9):532-9.
261. Domingues RB, Kuster GW, Onuki de Castro FL, Souza VA, Levi JE, Pannuti CS. Headache features in patients with dengue virus infection. Cephalalgia : an international journal of headache. 2006;26(7):879-82.
262. Galli F, D'Antuono G, Tarantino S, Viviano F, Borrelli O, Chirumbolo A, et al. Headache and recurrent abdominal pain: a controlled study by the means of the Child Behaviour Checklist (CBCL). Cephalalgia : an international journal of headache. 2007;27(3):211-9.
263. Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL. Economic burden of endometriosis (Brief record). Fertility and Sterility. 2006;86(6):1561-1572.
264. Hulme PA. Symptomatology and health care utilization of women primary care patients who experienced childhood sexual abuse [PhD's thesis]: University of Iowa; 1997. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2004110411&loginpage=Login.asp&site=ehost-live&scope=site
265. Jafari S, Amanlou M, Borhan Mojabi K, Farsam H. Comparative study of Zataria multiflora and Anthemis nobelis extracts with Myrthus communis preparation in the treatment of recurrent aphthous stomatitis. Daru: Journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2003;11(1):23-27.
266. Jani K. Prospective randomized study of internal oblique aponeurotic flap repair for tension-free reinforcement of the posterior inguinal wall: a new technique. International surgery. 2005;90(3):155-9.
267. Kang JC, Chung MH, Chao PC, Yeh CC, Hsiao CW, Lee TY, et al. Hand-assisted laparoscopic colectomy vs open colectomy: a prospective randomized study. Surgical endoscopy. 2004;18(4):577-81.
268. Ladwig KH, Hoberg E, Busch R. [Psychological comorbidity in patients with alarming chest pain symptoms]. Psychother Psychosom Med Psychol. 1998 Feb;48(2):46-54.
269. Linde M, Mellberg A, Dahlöf C. The natural course of migraine attacks. A prospective analysis of untreated attacks compared with attacks treated with a triptan. Cephalalgia : an international journal of headache. 2006;26(6):712-21.
270. Magnaval JF. [New elements in the symptomatology of visceral larva migrans]. Presse Med. 1987 Feb 7;16(4):151-4.

271. Mannix LK, Loder E, Nett R, Mueller L, Rodgers A, Hustad CM, et al. Rizatriptan for the acute treatment of ICHD-II proposed menstrual migraine: two prospective, randomized, placebo-controlled, double-blind studies. Cephalalgia : an international journal of headache. 2007;27(5):414-21.
272. Mathisen L, Andersen MH, Hol PK, Lingaas PS, Lundblad R, Rein KA, et al. Patient-reported outcome after randomization to on-pump versus off-pump coronary artery surgery. The Annals of thoracic surgery. 2005;79(5):1584-9.
273. Mathus-Vliegen EMH, Van Halteren H, Tytgat GN. Malignant lymphoma in coeliac disease: Various manifestations with distinct symptomatology and prognosis? Journal of Internal Medicine. 1994;236(1):43-49.
274. Meister W, Neiss A, Gross G, Doerr H, Hobel W, Malin J, et al. Demography, symptomatology, and course of disease in ambulatory zoster patients. A physician-based survey in Germany. Intervirology. 1998;41(6):272-7. doi: 24949
275. Mirkin D, Murphy Barron C, Iwasaki K. Actuarial analysis of private payer administrative claims data for women with endometriosis (Brief record). Journal of Managed Care Pharmacy. 2007;13(3):262-272.
276. Mökleby K, Blomhoff S, Malt UF, Dahlström A, Tauböll E, Gjerstad L. Psychiatric comorbidity and hostility in patients with psychogenic nonepileptic seizures compared with somatoform disorders and healthy controls. Epilepsia. 2002;43(2):193-198. doi: 10.1046/j.1528-1157.2002.20901.x
277. Nakipo, lu GF, Dogan Aslan M, Ozgirgin N. Evaluation of upper extremity rehabilitation in hemiplegic patients with and without complex regional pain syndrome type 1. International journal of rehabilitation research. Internationale Zeitschrift für Rehabilitationsforschung. Revue internationale de recherches de réadaptation. 2008;31(1):105-9.
278. Nobre ME, Leal AJ, Filho PM. Investigation into sleep disturbance of patients suffering from cluster headache. Cephalalgia : an international journal of headache. 2005;25(7):488-92.
279. Özen A, Ertem D, Pehlivanoglu E. Natural history and symptomatology of Helicobacter pylori in childhood and factors determining the epidemiology of infection. Journal of Pediatric Gastroenterology and Nutrition. 2006;42(4):398-404. doi: 10.1097/01.mpg.0000215307.48169.7b
280. Pilotto A, Franceschi M, Leandro G, Bozzola L, Fortunato A, Rassu M, et al. Efficacy of 7 day lansoprazole-based triple therapy for Helicobacter pylori infection in elderly patients. Journal of gastroenterology and hepatology. 1999;14(5):468-75.
281. Prior JO, Monbaron D, Koehli M, Calcagni ML, Ruiz J, Bischof Delaloye A. Prevalence of symptomatic and silent stress-induced perfusion defects in diabetic patients with suspected coronary artery disease referred for myocardial perfusion scintigraphy. European journal of nuclear medicine and molecular imaging. 2005;32(1):60-9.
282. Puzziferri N, Austrheim Smith IT, Wolfe BM, Wilson SE, Nguyen NT. Three-year follow-up of a prospective randomized trial comparing laparoscopic versus open gastric bypass. Annals of surgery. 2006;243(2):181-8.
283. Bazil CW. Comprehensive care of the epilepsy patient - Control, comorbidity, and cost. Epilepsia. 2004;45(SUPPL. 6):3-12. doi: 10.1111/j.0013-9580.2004.455002.x
284. Blecker U, Hauser B, Lanciers S, Keymolen K, Vandenplas Y. Symptomatology of Helicobacter pylori infection in children. Acta Paediatrica, International Journal of Paediatrics. 1996;85(10):1156-1158.
285. Bogetto F, Maina G, Ferro G, Carbone M, Gandolfo S. Psychiatric comorbidity in patients with burning mouth syndrome. Psychosomatic Medicine. 1998;60(3):378-385.
286. Cao J, Guo R, Xiong H, Hou X. Correlations among quality of life, life events and symptomatology in patients with functional dyspepsia. Chinese Journal of Gastroenterology. 2006;11(4):229-232.
287. Rosengren A, Hagman M, Pennert K, Wilhelmsen L. Clinical course and symptomatology of angina pectoris in a population study. Acta Medica Scandinavica. 1986;220(2):117-126.
288. Aigner M, Forster-Streffleur S, Prause W, Freidl M, Weiss M, Bach M. What does the WHOQOL-Bref measure? Measurement overlap between quality of life and depressive symptomatology in chronic somatoform pain disorder. Soc Psychiatry Psychiatr Epidemiol. 2006 Jan;41(1):81-6. doi: 10.1007/s00127-005-0997-8
289. Cheng HC, Chen HY, Tsai CL, Chen YJ, Cherng RJ. Comorbidity of motor and language impairments in preschool children of Taiwan. Res Dev Disabil. 2009 Sep-Oct;30(5):1054-61. doi: 10.1016/j.ridd.2009.02.008
290. De Toma G, Codacci-Pisanelli M, Nicolanti V, Plocco M, Caterino S, Perno CF. Obstructive biliary symptomatology as the first sign of HIV-infection. J Exp Clin Cancer Res. 1999 Dec;18(4):459-62.
291. Frese A, Eikermann A, Frese K, Schwaag S, Husstedt IW, Evers S. Headache associated with sexual activity: demography, clinical features, and comorbidity. Neurology. 2003 Sep 23;61(6):796-800.
292. Grace V, Zondervan K. Chronic pelvic pain in women in New Zealand: Comparative well-being, comorbidity, and impact on work and other activities. Health Care for Women International. 2006;27(7):585-599. doi: 10.1080/07399330600803725
293. Granderath FA, Kamolz T, Granderath UM, Pointner R. Gas-related symptoms after laparoscopic 360 degrees Nissen or 270 degrees Toupet fundoplication in gastrooesophageal reflux disease patients with aerophagia as comorbidity. Dig Liver Dis. 2007 Apr;39(4):312-8. doi: 10.1016/j.dld.2006.11.011
294. Hocaoglu C, Gulec MY, Durmus I. Psychiatric comorbidity in patients with chest pain without a cardiac etiology. Isr J Psychiatry Relat Sci. 2008;45(1):49-54.

295. Hubbard J, Realmuto GM, Northwood AK, Masten AS. Comorbidity of psychiatric diagnoses with posttraumatic stress disorder in survivors of childhood trauma. J Am Acad Child Adolesc Psychiatry. 1995 Sep;34(9):1167-73. doi: 10.1097/00004583-199509000-00014
296. Kolotylo CJ, Broome ME. Exploration of migraine pain, disability, depressive symptomatology, and coping: a pilot study. Health Care Women Int. 2000 Apr-May;21(3):203-18. doi: 10.1080/073993300245267
297. Kugler CF, Rudofsky G. Do age and comorbidity affect quality of life or PTA-induced quality-of-life improvements in patients with symptomatic pad? J Endovasc Ther. 2005 Jun;12(3):387-93. doi: 10.1583/04-1449.1
298. Leniger T, von den Driesch S, Isbruch K, Diener HC, Hufnagel A. Clinical characteristics of patients with comorbidity of migraine and epilepsy. Headache. 2003 Jun;43(6):672-7.
299. Lustyk MK, Widman L, Becker Lde L. Abuse history and premenstrual symptomatology: assessing the mediating role of perceived stress. Women Health. 2007;46(4):61-80.
300. Matsui K, Goldman L, Johnson PA, Kuntz KM, Cook EF, Lee TH. Comorbidity as a correlate of length of stay for hospitalized patients with acute chest pain. J Gen Intern Med. 1996 May;11(5):262-8.
301. Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. Neurology. 1994 Nov;44(11):2105-10.
302. Ottman R, Lipton RB. Is the comorbidity of epilepsy and migraine due to a shared genetic susceptibility? Neurology. 1996 Oct;47(4):918-24.
303. Reifen R, Rasooly I, Drumm B, Murphy K, Sherman P. Helicobacter pylori infection in children. Is there specific symptomatology? Dig Dis Sci. 1994 Jul;39(7):1488-92.
304. Sillanpää M, Aro H. Headache in teenagers: Comorbidity and prognosis. Functional Neurology. 2000;15(Suppl 3):116-121.
305. Strömgren AS, Sjogren P, Goldschmidt D, Petersen MA, Pedersen L, Groenvold M. Symptom priority and course of symptomatology in specialized palliative care. Journal of Pain and Symptom Management. 2006;31(3):199-206. doi: 10.1016/j.jpainsymman.2005.07.007
306. Adewuya AO, Loto OM, Adewumi TA. Pattern and correlates of premenstrual symptomatology amongst Nigerian University students. Journal of Psychosomatic Obstetrics and Gynecology. 2009;30(2):127-132. doi: 10.1080/01674820802545446
307. Baratta L, Gentile R, Coppotelli L, Tubani L, Paradiso M, Maffeo N, et al. The prevalence of arrhythmias in subjects over 80 years old. The prognostic role of anamnestic symptomatology and the therapeutic directions. Prevalenza dei disturbi del ritmo in soggetti di oltre 80 anni. Ruolo predittivo della sintomatologia anamnestica e orientamenti terapeutici. 1993;142(1):29-33.
308. Beutel ME, Weidner W, Brähler E. [Chronic pelvic pain and its comorbidity]. Der Urologe. Ausg. A. 2004;43(3):261-7.
309. Fleet RP, Dupuis G, Marchand A, Burelle D, Arsenault A, Beitman BD. Panic disorder in emergency department chest pain patients: Prevalence, comorbidity, suicidal ideation, and physician recognition. American Journal of Medicine. 1996;101(4):371-380. doi: 10.1016/s0002-9343(96)00224-0
310. Johansen A, Høilund-Carlsen PF, Christensen HW, Vach W, Møldrup M, Haghfelt T. Use of myocardial perfusion imaging to predict the effectiveness of coronary revascularisation in patients with stable angina pectoris. European journal of nuclear medicine and molecular imaging. 2005;32(12):1363-70.
311. Taal LA, Faber AW. Burn injuries, pain and distress: exploring the role of stress symptomatology. Burns. 1997 Jun;23(4):288-90.
312. Witting K, Santtila P, Rijsdijk F, Varjonen M, Jern P, Johansson A, et al. Correlated genetic and non-shared environmental influences account for the co-morbidity between female sexual dysfunctions. Psychol Med. 2009 Jan;39(1):115-27. doi: 10.1017/s0033291708003206
313. Zencir M, Ergin H, Şahiner T, Kiliç I, Alkiş E, Özdel L, et al. Epidemiology and symptomatology of migraine among school children: Denizli urban area in Turkey. Headache. 2004;44(8):780-785. doi: 10.1111/j.1526-4610.2004.04145.x
314. Ballard KD, Seaman HE, De Vries CS, Wright JT. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case-control study - Part 1. BJOG: An International Journal of Obstetrics and Gynaecology. 2008;115(11):1382-1391. doi: 10.1111/j.1471-0528.2008.01878.x
315. Lutgendorf SK, Kreder KJ, Rothrock NE, Ratliff TL, Zimmerman B. Stress and symptomatology in patients with interstitial cystitis: A laboratory stress model. Journal of Urology. 2000;164(4):1265-1269.
316. Marana R, Muzii L, Caruana P, Dell'Acqua S, Mancuso S. Evaluation of the correlation between endometriosis extent, age of the patients and associated symptomatology. Acta Europaea Fertilitatis. 1991;22(4):209-212.
317. Migraine epidemiology, clinical presentations, and comorbidity. Headache: The Journal of Head & Face Pain. 2004 07;44(7):734-735.
318. Bani, M., Sutli, Z., Biocina B, Kujundzi, et al. Peptic ulcer disease in dyspeptic patients with ischemic heart disease: search and treat? Zeitschrift für Gastroenterologie. 2005;43(6):581-6.
319. Bøe MG, Salvesen R, Mygland A. Chronic daily headache with medication overuse: a randomized follow-up by neurologist or PCP. Cephalalgia : an international journal of headache. 2009;29(8):855-63.
320. Cady R, Martin V, Mauskop A, Rodgers A, Hustad CM, Ramsey KE, et al. Symptoms of cutaneous

sensitivity pre-treatment and post-treatment: results from the rizatriptan TAME studies. Cephalalgia : an international journal of headache. 2007;27(9):1055-60.
321. Dorn LD, Campo JC, Thato S, Dahl RE, Lewin D, Chandra R, et al. Psychological comorbidity and stress reactivity in children and adolescents with recurrent abdominal pain and anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2003 Jan;42(1):66-75. doi: 10.1097/00004583-200301000-00012
322. Kapetanopoulos A, Heller GV, Selker HP, Ruthazer R, Beshansky JR, Feldman JA, et al. Acute resting myocardial perfusion imaging in patients with diabetes mellitus: results from the Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain (ERASE Chest Pain) trial. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2004;11(5):570-7.
323. Kolotylo C, MacDonald JM. Exploration of the relationships among personal and illness-related factors, migraine headache pain, the chronic pain experience, coping, depressive symptomatology, disability, and quality of life in women with migraine headache [PhD's thesis]: University of Wisconsin - Milwaukee; 1999. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2005056724&loginpage=Login.asp&site=ehost-live&scope=site
324. Mielck A, Reisig V, Rathmann W, Group KS. Health inequalities among persons with type 2 diabetes: the example of intermittent claudication. Gesundheitswesen (Bundesverband der Ärzte des Öffentlichen Gesundheitsdienstes (Germany)). 2005;67(S01):137-143. doi: 10.1055/s-2005-858230
325. Rabeneck L, Cook KF, Wristers K, Souchek J, Menke T, Wray NP. SODA (severity of dyspepsia assessment): a new effective outcome measure for dyspepsia-related health. Journal of clinical epidemiology. 2001;54(8):755-65.
326. Sinkovic A, Marinsek M, Svensek F. Women and men with unstable angina and/or non-ST-elevation myocardial infarction. Wiener klinische Wochenschrift. 2006;118 (Suppl 2):52-7. doi: 10.1007/s00508-006-0553-x
327. Tölg R, Witt M, Schwarz B, Kurz T, Kurowski V, Hartmann F, et al. Comparison of carvedilol and metoprolol in patients with acute myocardial infarction undergoing primary coronary intervention--the PASSAT Study. Clinical research in cardiology : official journal of the German Cardiac Society. 2006;95(1):31-41.
328. Usai P, Manca R, Cuomo R, Lai MA, Boi MF. Effect of gluten-free diet and co-morbidity of irritable bowel syndrome-type symptoms on health-related quality of life in adult coeliac patients. Digestive and Liver Disease. 2007;39(9):824-828. doi: 10.1016/j.dld.2007.05.017
329. Walfridsson U, Strömberg A, Janzon M, Walfridsson H. Wolff-Parkinson-White syndrome and atrioventricular nodal re-entry tachycardia in a Swedish population: consequences on health-related quality of life. Pacing and clinical electrophysiology : PACE. 2009;32(10):1299-306.
330. Welén K, Faresjö A, Faresjö T. Functional dyspepsia affects women more than men in daily life: a case-control study in primary care. Gender medicine : official journal of the Partnership for Gender Specific Medicine at Columbia University. 2008;5(1):62-73.
331. Wewer V, Andersen LP, Pærregaard A, Gernow AB, Hart Hansen JP, Matzen P, et al. The prevalence and related symptomatology of Helicobacter pylori in children with recurrent abdominal pain. Acta Paediatrica, International Journal of Paediatrics. 1998;87(8):830-835. doi: 10.1080/080352598750013581
332. Wymer JP, Simpson J, Sen D, Bongardt S, Lacosamide SPSG. Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double-blind placebo-controlled trial of fixed-dose regimens. The Clinical journal of pain. 2009;25(5):376-85.
333. Hassett AL, Radvanski DC, Buyske S, Savage SV, Gara M, Escobar JI, et al. Role of psychiatric comorbidity in chronic lyme disease. Arthritis Care and Research. 2008;59(12):1742-1749. doi: 10.1002/art.24314
334. Sicard GA, Reilly JM, Rubin BG, Thompson RW, Allen BT, Flye MW, et al. Transabdominal versus retroperitoneal incision for abdominal aortic surgery: report of a prospective randomized trial. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 1995;21(2):174-81; discussion 181-3.
335. Wojczynski MK. Characteristics of the co-morbidity of Irritable Bowel Syndrome: A secondary analysis of existing twin data. Dissertation Abstracts International: Section B: The Sciences and Engineering Vol. 2006;67(2-B):843. Available from: PsycINFO.
336. Annagur A, Annagur BB, Sahin A, Ors R, Kara F. Is maternal depressive symptomatology effective on success of exclusive breastfeeding during postpartum 6 weeks? Breastfeed Med. 2013 Feb;8(1):53-7. doi: 10.1089/bfm.2012.0036
337. Chivers ML, Pittini R, Grigoriadis S, Villegas L, Ross LE. The relationship between sexual functioning and depressive symptomatology in postpartum women: a pilot study. J Sex Med. 2011 Mar;8(3):792-9. doi: 10.1111/j.1743-6109.2010.02154.x
338. Ecevit CO, Özgenç F, Yüksekkaya HA, Ünal F, Arikan C, Yağci RV. Peptic ulcer disease in children: An uncommon disorder with subtle symptomatology. Turkish Journal of Gastroenterology. 2012;23(6):666-669.
339. Gil FF, Barros MJ, Macedo NA, Júnior CGE, Redoan R, Busatti H, et al. Prevalence of intestinal parasitism and associated symptomatology among hemodialysis patients. Prevalência de parasitismo intestinal e

sintomatologia associada em pacientes hemodialíticos. 2013;55(2):69-74.
340. Heddini U, Bohm-Starke N, Nilsson KW, Johannesson U. Provoked vestibulodynia--medical factors and comorbidity associated with treatment outcome. J Sex Med. 2012 May;9(5):1400-6. doi: 10.1111/j.1743-6109.2012.02665.x
341. Hoogwegt MT, Kupper N, Jordaens L, Pedersen SS, Theuns DA. Comorbidity burden is associated with poor psychological well-being and physical health status in patients with an implantable cardioverter-defibrillator. Europace. 2013 Apr 21;15(10):1468-74. doi: 10.1093/europace/eut072
342. Jette N, Patten S, Williams J, Becker W, Wiebe S. Comorbidity of migraine and psychiatric disorders--A national population-based study. Headache: The Journal of Head and Face Pain. 2008;48(4):501-516. Available from: PsycINFO. doi: 10.1111/j.1526-4610.2007.00993.x
343. Jodoin M, Bergeron S, Khalife S, Dupuis MJ, Desrochers G, Leclerc B. Attributions about pain as predictors of psychological symptomatology, sexual function, and dyadic adjustment in women with vestibulodynia. Arch Sex Behav. 2011 Feb;40(1):87-97. doi: 10.1007/s10508-010-9647-7
344. Joseph S, Moore BT, Sorensen GB, Earley JW, Tang F, Jones P, et al. Single-incision laparoscopic cholecystectomy: a comparison with the gold standard (Provisional abstract). Surgical Endoscopy. 2011;25(9):3008-15. doi: 10.1007/s00464-011-1661-x
345. Klarenbeek BR, Bergamaschi R, Veenhof AA, Peet DL, Broek WT, Lange ES, et al. Laparoscopic versus open sigmoid resection for diverticular disease: follow-up assessment of the randomized control Sigma trial. Surgical endoscopy [Comparative Study; Multicenter Study; Randomized Controlled Trial]. 2011;25(4):1121-6. doi: 10.1007/s00464-010-1327-0
346. Lamino DDA, Mota DDCDF, Pimenta CADM. Prevalence and comorbidity of pain and fatigue in women with breast cancer. Revista da Escola de Enfermagem. 2011;45(2):496-502.
347. Mieres JH, Heller GV, Hendel RC, Gulati M, Boden WE, Katten D, et al. Signs and symptoms of suspected myocardial ischemia in women: results from the What is the Optimal Method for Ischemia Evaluation in WomeN? Trial. J Womens Health (Larchmt) [Multicenter Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2011;20(9):1261-8. doi: 10.1089/jwh.2010.2595
348. Radat F, Sakh D, Lutz G, El Amrani M, Ferreri M, Bousser M-G. Psychiatric comorbidity is related to headache induced by chronic substance use in migraineurs. Headache: The Journal of Head and Face Pain. 1999;39(7):477-480. Available from: PsycINFO. doi: 10.1046/j.1526-4610.1999.3907477.x
349. Rodriguez-Cerrillo M, Poza-Montoro A, Fernandez-Diaz E, Romero AI. Patients with uncomplicated diverticulitis and comorbidity can be treated at home. Eur J Intern Med. 2010 Dec;21(6):553-4. doi: 10.1016/j.ejim.2010.09.002
350. Ryerson CJ, Arean PA, Berkeley J, Carrieri-Kohlman VL, Pantilat SZ, Landefeld CS, et al. Depression is a common and chronic comorbidity in patients with interstitial lung disease. Respirology. 2012 Apr;17(3):525-32. doi: 10.1111/j.1440-1843.2011.02122.x
351. Lesnik Oberstein S, van den Boom R, Middelkoop H, Ferrari M, Knaap Y, van Houwelingen H, et al. Migraine: epidemiology, genetics, and comorbidity. Headache: The Journal of Head & Face Pain. 2004;44(4):379-381. Available from: s3h.
352. Sakai H, Kawamura C, Cardenas X, Ohashi K. Premenstrual and menstrual symptomatology in young adult Japanese females who smoke tobacco. J Obstet Gynaecol Res. 2011 Apr;37(4):325-30. doi: 10.1111/j.1447-0756.2010.01353.x
353. Samantha MB, Leserman J. Psychiatric comorbidity in women with chronic pelvic pain. CNS Spectrums. 2011;16(2):29-35. doi: 10.1017/S1092852912000156
354. Turk DC, Audette J, Levy RM, Mackey SC, Stanos S. Assessment and Treatment of Psychosocial Comorbidities in Patients With Neuropathic Pain. Mayo Clinic Proceedings (Science Direct). 2010;85(3):S42-S50.
355. Wieser T, Dresler K, Evers S, Gaul C, König D, Hölzl D, et al. No influence of 5-HTTLPR gene polymorphism on migraine symptomatology, comorbid depression, and chronification. Headache: The Journal of Head and Face Pain. 2010;50(3):420-430. Available from: PsycINFO. doi: 10.1111/j.1526-4610.2009.01428.x
356. Zhang J, He ML, Li SW. [Clinical traits and treatment outcome for comorbidity of depression and neurological disorders]. Zhonghua Yi Xue Za Zhi. 2010 Dec 7;90(45):3180-3.
357. Han PY, Ezquerro R, Pan K-m, Hwang S, Chung Y, Lu J-J. Comorbidities associated with diabetic foot complications among Asian Americans in southern California. Journal of the American Podiatric Medical Association (JAPMA). 2003;93(1):37-41.
358. Rihn JA, Kurd M, Hilibrand AS, Lurie J, Zhao W, Albert T, et al. The influence of obesity on the outcome of treatment of lumbar disc herniation: analysis of the Spine Patient Outcomes Research Trial (SPORT). The Journal of bone and joint surgery. American volume [Multicenter Study; Randomized Controlled Trial; Research Support, N.I.H., Extramural; Research Support, U.S. Gov't, P.H.S.]. 2013;95(1):1-8. doi: 10.2106/JBJS.K.01558
359. Xiong GL, Fiuzat M, Kuchibhatla M, Krishnan R, O'Connor CM, Jiang W. Health status and depression remission in patients with chronic heart failure: patient-reported outcomes from the SADHART-CHF trial. Circulation. Heart failure [Randomized Controlled Trial; Research Support, N.I.H., Extramural]. 2012;5(6):688-92. doi: 10.1161/CIRCHEARTFAILURE.112.967620

360. Olaya-Contreras P, Styf J. Biopsychosocial function analyses changes the assessment of the ability to work in patients on long-term sick-leave due to chronic musculoskeletal pain: The role of undiagnosed mental health comorbidity. Scandinavian Journal of Public Health. 2013;41(3):247-255. Available from: PsycINFO.
361. Tamari K. Baseline comorbidity associated with the short-term effects of exercise intervention on quality of life in the Japanese older population: an observational study. Arch Phys Med Rehabil. 2010 Sep;91(9):1363-9. doi: 10.1016/j.apmr.2010.06.014
362. Simunic M, Ljutic D, Mise S, Pesutic-Pisac V, Tonkic M, Hozo I. Helicobacter pylori eradication for the treatment of dyspeptic symptoms in chronic renal failure. Annals of Saudi medicine. 2005;25(5):425-7.
363. Bachmann GA, Rosen R, Finn VW, Utian WH, Ayers C, Basson R, et al. Vulvodynia: A state-of-the-art consensus on definitions, diagnosis and management. Journal of Reproductive Medicine for the Obstetrician and Gynecologist. 2006;51(6):447-56.
364. Cassidy JD, Boyle E, Cote P, He Y, Hogg-Johnson S, Silver FL. Risk of vertebrobasilar stroke and chiropractic care: results of a population-based case-control and case-crossover study. Spine. 2008;33(4 Suppl):S176-83. doi: 10.1097/BRS.0b013e3181644600
365. Brar P, Jain S, Singh I. Complications of Axillary Lymph Node Dissection in Treatment of Early Breast Cancer: A Comparison of MRM and BCS. Indian Journal of Surgical Oncology. 2011;2(2):126-32. doi: 10.1007/s13193-011-0078-2
366. Cronin J, Livhits M, Mercado C, Chen F, Foster N, Chandler C, et al. Quality improvement pilot program for vulnerable elderly surgical patients. American surgeon. 2011;77(10):1305-8.
367. Hamedi B, Omidvar A, Dehbashi S, Alborzi S, Alborzi M. A comparison of the effect of short-term aromatase inhibitor (letrozole) and GnRH agonist (triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis. Archives of gynecology and obstetrics. 2011;284(1):105-10. doi: 10.1007/s00404-010-1599-6
368. Wasay M, Khealani B, Yousuf A, Azam I, Rathi SL, Malik A, et al. Knowledge gaps in stroke care: Results of a survey of family physicians in Pakistan. Journal of stroke and cerebrovascular diseases. 2011;20(4):282-6. doi: 10.1016/j.jstrokecerebrovasdis.2010.01.010
369. Bradley JF, Williams KB, Wormer BA, Tsirline VB, Walters AL, Sing RF, et al. Preliminary results of surgical and quality of life outcomes of Physiomesh in an international, prospective study. Surgical technology international. 2012;22:113-9.
370. Breslau N, Schultz L, Lipton R, Peterson E, Welch KMA. Migraine headaches and suicide attempt. Headache. 2012;52(5):723-31. doi: 10.1111/j.1526-4610.2012.02117.x
371. Cassia Peniche A. Use of Calatonia during the immediate postoperative period: A randomised clinical trail. European Journal of Integrative Medicine. 2012;4:118. doi: 10.1016/j.eujim.2012.07.748
372. Corli O, Montanari M, Deandrea S, Greco MT, Villani W, Apolone G. An exploratory analysis on the effectiveness of four strong opioids in patients with cancer pain. Pain medicine (Malden, Mass.). 2012;13(7):897-907. doi: 10.1111/j.1526-4637.2012.01408.x
373. Karas J, Chang K, Denoya P, Fakhoury M, Fakhoury J, Stein S, et al. Doppler-guided transanal haemorrhoidal dearterialisation with mucopexy versus Ferguson haemorrhoidectomy for Grade III or IV haemorrhoids: Short-term results of a single blind randomized controlled trial. Colorectal disease. 2012;14(1):1. doi: 10.1111/j.1463-1318.2012.03153.x
374. Yamaguchi T, Morita T, Shinjo T, Inoue S, Takigawa C, Aruga E, et al. Effect of parenteral hydration therapy based on the Japanese national clinical guideline on quality of life, discomfort, and symptom intensity in patients with advanced cancer. Journal of pain and symptom management. 2012;43(6):1001-12. doi: 10.1016/j.jpainsymman.2011.06.028
375. Abernethy AP, Currow DC, Shelby-James T, Rowett D, May F, Samsa GP, et al. Delivery strategies to optimize resource utilization and performance status for patients with advanced life-limiting illness: results from the "palliative care trial" [ISRCTN 81117481]. Journal of pain and symptom management. 2013;45(3):488-505. doi: 10.1016/j.jpainsymman.2012.02.024
376. Bener A, Al-Kazaz M, Ftouni D, Al-Harthy M, Dafeeah EE. Diagnostic overlap of depressive, anxiety, stress and somatoform disorders in primary care. Asia-Pacific Psychiatry. 2013;5(1):E29-e38. doi: 10.1111/j.1758-5872.2012.00215.x
377. Esguerra-Gonzalez A, Ilagan-Honorio M, Fraschilla S, Kehoe P, Lee AJ, Marcarian T, et al. CNE article: pain after lung transplant: high-frequency chest wall oscillation vs chest physiotherapy. American journal of critical care. 2013;22(2):115-24. doi: 10.4037/ajcc2013869
378. Espinosa G, Annapragada A. Cost-effectiveness of a novel blood-pool contrast agent in the setting of chest pain evaluation in an emergency department. AJR American Journal of Roentgenology. 2013;201(4):710-719. doi: 10.2214/AJR.12.9946
379. Henzler T, Gruettner J, Meyer M, Rothhaar B, Apfaltrer P, Metzger F, et al. Coronary computed tomography and triple rule out CT in patients with acute chest pain and an intermediate cardiac risk for acute coronary syndrome: Part 2: economic aspects. European Journal of Radiology. 2013;82(1):106-111. doi: 10.1016/j.ejrad.2012.06.012
380. Hofsø K, Rustøen T, Cooper BA, Bjordal K, Miaskowski C. Changes over time in occurrence, severity,

and distress of common symptoms during and after radiation therapy for breast cancer. Journal of pain and symptom management. 2013;45(6):980-1006. doi: 10.1016/j.jpainsymman.2012.06.003
381. Misra UK, Kalita J, Bhoi SK. Allodynia in migraine: clinical observation and role of prophylactic therapy. Clinical journal of pain. 2013;29(7):577-82. doi: 10.1097/AJP.0b013e31826b130f
382. Radat F, Margot-Duclot A, Attal N. Psychiatric co-morbidities in patients with chronic peripheral neuropathic pain: A multicentre cohort study. European Journal of Pain. 2013;17(10):1547-1557. Available from: PsycINFO.
383. Brawman-Mintzer O, Durkalski V, Wu Q, Romagnuolo J, Fogel E, Tarnasky P, et al. Psychosocial characteristics and pain burden of patients with suspected sphincter of Oddi dysfunction in the EPISOD multicenter trial. The American journal of gastroenterology. 2014;109(3):436-42. doi: 10.1038/ajg.2013.467
384. Ducrotte P, Grimaud JC, Dapoigny M, Personnic S, O'Mahony V, Andro-Delestrain MC. On-demand treatment with alverine citrate/simeticone compared with standard treatments for irritable bowel syndrome: Results of a randomised pragmatic study. International journal of clinical practice. 2014;68(2):245-54. doi: 10.1111/ijcp.12333
385. Escribano J, Balaguer A, Roqué i Figuls M, Feliu A, Ferre N. Dietary interventions for preventing complications in idiopathic hypercalciuria. Cochrane Database of Systematic Reviews. 2014 (2):CD006022. doi: 10.1002/14651858.CD006022.pub4
386. Johnston MJ, Fitzgerald JEF, Bhangu A, Greaves NS, Prew CL, Fraser I. Outpatient management of biliary colic: A prospective observational study of prescribing habits and analgesia effectiveness. International journal of surgery (London, England). 2014;12(2):169-76. doi: 10.1016/j.ijsu.2013.12.003
387. Lee MH, Wu HC, Lin JY, Tan TH, Chan PC, Chen YF. Development and evaluation of an E-health system to care for patients with bladder pain syndrome/interstitial cystitis. International journal of urology. 2014;21(S1):62-8. doi: 10.1111/iju.12336
388. McDermott MJ, Tull MT, Gratz KL, Houle TT, Smitherman TA. Comorbidity of migraine and psychiatric disorders among substance‐dependent inpatients. Headache: The Journal of Head and Face Pain. 2014;54(2):290-302. Available from: PsycINFO. doi: 10.1111/head.12171
389. Riegel B, Bruenahl CA, Ahyai S, Bingel U, Fisch M, Lowe B. Assessing psychological factors, social aspects and psychiatric co-morbidity associated with Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) in men -- a systematic review. J Psychosom Res. 2014 Nov;77(5):333-50. doi: 10.1016/j.jpsychores.2014.09.012
390. Simpson RJ, McLean G, Guthrie B, Mair F, Mercer SW. Physical and mental health comorbidity is common in people with multiple sclerosis: Nationally representative cross-sectional population database analysis. BMC Neurology. 2014;14(1):128. Available from: Scopus. doi: 10.1186/1471-2377-14-128
391. Sullivan AL, Beshansky JR, Ruthazer R, Murman DH, Mader TJ, Selker HP. Factors associated with longer time to treatment for patients with suspected acute coronary syndromes: a cohort study. Circulation. Cardiovascular quality and outcomes. 2014 (1):86-94. doi: 10.1161/CIRCOUTCOMES.113.000396
392. Vonk Noordegraaf A, Anema JR, Mechelen W, Knol DL, Baal WM, Kesteren PJM, et al. A personalised eHealth programme reduces the duration until return to work after gynaecological surgery: Results of a multicentre randomised trial. Bjog. 2014;121(9):1127-35. doi: 10.1111/1471-0528.12661
393. Akyildiz K, Sercan M, Yildiz N, Cevik A, Kiyan A. Is headache only headache? Comorbidity of headaches and mental disorders. Dusunen Adam. 2015;28(1):34-46. Available from: Scopus. doi: 10.5350/dajpn2015280104
394. Ozis SE, Unal Cevik I, Uslu HY, Ozdemir S, Gulpinar K, Aydin HT. The long-term changes in pain-related symptomatology of inguinal hernia following 2 different herniorrhaphy techniques. Turk J Med Sci. 2015;45(1):202-7.
395. Adigüzel H, Taşkin EO, Danaci AE. Manisa ılinde premenstrüel sendrom belirti örüntüsü ve belirti yayginliğinin araştirilmasi. Türk Psikiyatri Dergisi. 2007;18(3):215-222. Available from: PsycINFO.
396. Almeida JI, Kaufman J, Göckeritz O, Chopra P, Evans MT, Hoheim DF, et al. Radiofrequency endovenous ClosureFAST versus laser ablation for the treatment of great saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study). Journal of vascular and interventional radiology : JVIR. 2009;20(6):752-9.
397. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis and rheumatism. 2004;50(9):2974-84.
398. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005;119(1-3):5-15.
399. Arora R, Gabl M, Gschwentner M, Deml C, Krappinger D, Lutz M. A comparative study of clinical and radiologic outcomes of unstable colles type distal radius fractures in patients older than 70 years: nonoperative treatment versus volar locking plating. Journal of orthopaedic trauma. 2009;23(4):237-42.
400. Chassany O, Boureau F, Liard F, Bertin P, Serrie A, Ferran P, et al. Effects of training on general

practitioners' management of pain in osteoarthritis: a randomized multicenter study. The Journal of rheumatology. 2006;33(9):1827-34.
401. Dalichau S, Stein B, Schäfer K, Buhlmann JJ, Menken P. [Ultrasonic Quantification of spinal configuration and postural capacity for evaluation of different muscle strengthening programs in the therapy of back pain]. Zeitschrift für Orthopädie und ihre Grenzgebiete. 2005;143(1):79-85.
402. Donati G, Spinazzè R. [A clinical study to determine the optimal dosage of ST-679 in the treatment of rheumatic diseases]. La Clinica terapeutica. 1993;142(1 Pt 2):19-28.
403. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. Pain medicine (Malden, Mass.). 2006;7(3):237-42.
404. John MT, Dworkin SF, Mancl LA. Reliability of clinical temporomandibular disorder diagnoses. Pain. 2005;118(1-2):61-9.
405. Kroenke K, Messina N, Benattia I, Graepel J, Musgnung J. Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder. The Journal of clinical psychiatry. 2006;67(1):72-80.
406. Lemming D, Sörensen J, Graven Nielsen T, Arendt Nielsen L, Gerdle B. The responses to pharmacological challenges and experimental pain in patients with chronic whiplash-associated pain. The Clinical journal of pain. 2005;21(5):412-21.
407. Lemstra M, Olszynski WP. The effectiveness of standard care, early intervention, and occupational management in worker's compensation claims. Spine. 2003;28(3):299-304.
408. Manchikanti L, Pampati V, Damron KS, McManus CD, Jackson SD, Barnhill RC, et al. A randomized, prospective, double-blind, placebo-controlled evaluation of the effect of sedation on diagnostic validity of cervical facet joint pain. Pain Physician. 2004;7(3):301-9.
409. Mirzai H, Eminoglu M, Orguc S. Are drains useful for lumbar disc surgery? A prospective, randomized clinical study. Journal of spinal disorders & techniques. 2006;19(3):171-7.
410. Mongini F, Ciccone G, Rota E, Ferrero L, Ugolini A, Evangelista A, et al. Effectiveness of an educational and physical programme in reducing headache, neck and shoulder pain: a workplace controlled trial. Cephalalgia : an international journal of headache. 2008;28(5):541-52.
411. Paradiso R, Alexandre A. The different outcomes of patients with disc herniation treated either by microdiscectomy, or by intradiscal ozone injection. Acta neurochirurgica. Supplement. 2005;92:139-42.
412. Campbell R, Evans M, Tucker M, Quilty B, Dieppe P, Donovan JL. Why don't patients do their exercises? Understanding non-compliance with physiotherapy in patients with osteoarthritis of the knee. Journal of epidemiology and community health. 2001;55(2):132-8.
413. Iliffe S, Kharicha K, Carmaciu C, Harari D, Swift C, Gillman G, et al. The relationship between pain intensity and severity and depression in older people: exploratory study. BMC family practice. 2009;10:54. doi: 10.1186/1471-2296-10-54
414. Poulain P, Denier W, Douma J, Hoerauf K, Samija M, Sopata M, et al. Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. Journal of pain and symptom management. 2008;36(2):117-25.
415. Rades D, Lange M, Veninga T, Rudat V, Bajrovic A, Stalpers LJ, et al. Preliminary results of spinal cord compression recurrence evaluation (score-1) study comparing short-course versus long-course radiotherapy for local control of malignant epidural spinal cord compression. International journal of radiation oncology, biology, physics. 2009;73(1):228-34.
416. Rudick RA, Miller D, Hass S, Hutchinson M, Calabresi PA, Confavreux C, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. Annals of neurology. 2007;62(4):335-46.
417. Sarchielli P, Alberti A, Candeliere A, Floridi A, Capocchi G, Calabresi P. Glial cell line-derived neurotrophic factor and somatostatin levels in cerebrospinal fluid of patients affected by chronic migraine and fibromyalgia. Cephalalgia : an international journal of headache. 2006;26(4):409-15.
418. Saxler G, Wedemeyer C, von Knoch M, Render UM, Quint U. [Follow-up study after dynamic and static stabilisation of the lumbar spine]. Zeitschrift für Orthopädie und ihre Grenzgebiete. 2005;143(1):92-9.
419. Schell E, Theorell T, Hasson D, Arnetz B, Saraste H. Impact of a web-based stress management and health promotion program on neck-shoulder-back pain in knowledge workers? 12 month prospective controlled follow-up. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine. 2008;50(6):667-76.
420. Serafini G, Sconfienza LM, Lacelli F, Silvestri E, Aliprandi A, Sardanelli F. Rotator cuff calcific tendonitis: short-term and 10-year outcomes after two-needle us-guided percutaneous treatment--nonrandomized controlled trial. Radiology. 2009;252(1):157-64.
421. Tei Y, Morita T, Nakaho T, Takigawa C, Higuchi A, Suga A, et al. Treatment efficacy of neural blockade in specialized palliative care services in Japan: a multicenter audit survey. Journal of pain and symptom management. 2008;36(5):461-7.
422. Thompson JW, Bower S, Tyrer SP. A double blind randomised controlled clinical trial on the effect of transcutaneous spinal electroanalgesia (TSE) on low back pain. European journal of pain (London, England).

2008;12(3):371-7.
423. Thomson S, Jacques L. Demographic characteristics of patients with severe neuropathic pain secondary to failed back surgery syndrome. Pain practice : the official journal of World Institute of Pain. 2009;9(3):206-15.
424. Utne I, Miaskowski C, Bjordal K, Cooper BA, Valeberg BT, Rustøen T. Confirmatory factor analysis of the coping strategies questionnaire-revised in samples of oncology outpatients and inpatients with pain. The Clinical journal of pain. 2009;25(5):391-400.
425. Wasan AD, Kaptchuk TJ, Davar G, Jamison RN. The association between psychopathology and placebo analgesia in patients with discogenic low back pain. Pain medicine (Malden, Mass.). 2006;7(3):217-28.
426. Wegener ST, Mackenzie EJ, Ephraim P, Ehde D, Williams R. Self-management improves outcomes in persons with limb loss. Archives of physical medicine and rehabilitation. 2009;90(3):373-80.
427. Chappell AS, Littlejohn G, Kajdasz DK, Scheinberg M, D'Souza DN, Moldofsky H. A 1-year safety and efficacy study of duloxetine in patients with fibromyalgia. The Clinical journal of pain. 2009;25(5):365-75.
428. Defrin R, Ariel E, Peretz C. Segmental noxious versus innocuous electrical stimulation for chronic pain relief and the effect of fading sensation during treatment. Pain. 2005;115(1-2):152-60.
429. Desigan S, Hall Craggs MA, Ho CP, Eliahoo J, Porter JB. Degenerative disc disease as a cause of back pain in the thalassaemic population: a case-control study using MRI and plain radiographs. Skeletal radiology. 2006;35(2):95-102.
430. Dobscha SK, Corson K, Perrin NA, Hanson GC, Leibowitz RQ, Doak MN, et al. Collaborative care for chronic pain in primary care: a cluster randomized trial. JAMA : the journal of the American Medical Association. 2009;301(12):1242-52.
431. Druss BG, Rosenheck RA, Sledge WH. Health and disability costs of depressive illness in a major US corporation (Brief record). American Journal of Psychiatry. 2000;157(8):1274-1278.
432. Enthoven P, Skargren E, Oberg B. Clinical course in patients seeking primary care for back or neck pain: a prospective 5-year follow-up of outcome and health care consumption with subgroup analysis. Spine. 2004;29(21):2458-65.
433. Mangels M, Schwarz S, Worringen U, Holme M, Rief W. Evaluation of a behavioral-medical inpatient rehabilitation treatment including booster sessions: a randomized controlled study. The Clinical journal of pain. 2009;25(5):356-64.
434. O'Toole BI, Marshall RP, Schureck RJ, Dobson M. Posttraumatic stress disorder and comorbidity in Australian Vietnam veterans: Risk factors, chronicity and combat. Australian and New Zealand Journal of Psychiatry. 1998;32(1):32-42. doi: 10.1046/j.1440-1614.1998.00368.x
435. Peterson MG, Blake VA, Allegrante JP, Johanson NA, Mancuso CA, Robbins L, et al. A comparison of self-reported hip symptomatology in hip replacement patients and a population-based sample of medicare beneficiaries. Med Sci Monit. 2004 Jul;10(7):CR275-81.
436. Bailey RL, Ledikwe JH, Smiciklas-Wright H, Mitchell DC, Jensen GL. Persistent oral health problems associated with comorbidity and impaired diet quality in older adults. J Am Diet Assoc. 2004 Aug;104(8):1273-6. doi: 10.1016/j.jada.2004.05.210
437. Bock JJ, Maurer P, Fuhrmann RA. The importance of temporomandibular function for patient satisfaction following orthognathic surgery. Journal of orofacial orthopedics = Fortschritte der Kieferorthopädie : Organ/official journal Deutsche Gesellschaft für Kieferorthopädie. 2007;68(4):299-307.
438. Maes M, Mihaylova I, Kubera M, Leunis JC. An IgM-mediated immune response directed against nitro-bovine serum albumin (nitro-BSA) in chronic fatigue syndrome (CFS) and major depression: Evidence that nitrosative stress is another factor underpinning the comorbidity between major depression and CFS. Neuroendocrinology Letters. 2008;29(3):313-319.
439. van Grootel RJ, van der Glas HW, Buchner R, de Leeuw JR, Passchier J. Patterns of pain variation related to myogenous temporomandibular disorders. The Clinical journal of pain. 2005;21(2):154-65.
440. Routine physiotherapy is as effective as one advice and assessment session for reducing disability in people with low back pain. Evidence based Healthcare & Public Health. 2005;9(2):129-30.
441. Abdu WA. Comorbidity with low back pain. A cross-sectional population based survey of 12- to 22-year-olds: Point of view. Spine. 2004;29(13):1492. doi: 10.1097/01.brs.0000129030.04443.60
442. Almog G, Lamond PJ, Gosselin G. Effects of chiropractic care on spinal symptomatology among professional drivers: A pilot study. Clinical Chiropractic. 2004;7(3):114-119. doi: 10.1016/j.clch.2004.05.005
443. Cleves MA, Sanchez N, Draheim M. Evaluation of two competing methods for calculating Charlson's comorbidity index when analyzing short-term mortality using administrative data. J Clin Epidemiol. 1997 Aug;50(8):903-8.
444. Di Bari M, Virgillo A, Matteuzzi D, Inzitari M, Mazzaglia G, Pozzi C, et al. Predictive validity of measures of comorbidity in older community dwellers: The Insufficienza Cardiaca negli Anziani Residenti a Dicomano study. Journal of the American Geriatrics Society. 2006;54(2):210-216. doi: 10.1111/j.1532-5415.2005.00572.x
445. Ford JD, Campbell KA, Storzbach D, Binder LM, Anger WK, Rohlman DS. Posttraumatic stress symptomatology is associated with unexplained illness attributed to Persian Gulf War military service. Psychosom Med. 2001 Sep-Oct;63(5):842-9.

446. Fortnum HM, Marshall DH, Summerfield AQ. Epidemiology of the UK population of hearing-impaired children, including characteristics of those with and without cochlear implants - Audiology, aetiology, comorbidity and affluence. International Journal of Audiology. 2002;41(3):170-179.
447. Higginson AP, Braybrook J, Williams S, Finlay D. Isolated scaphotrapeziotrapezoid osteoarthritis: Prevalence, symptomatology and associated scapholunate ligament disruption in a population presenting to an accident and emergency department with acute wrist injuries. Clinical Radiology. 2001;56(5):372-374. doi: 10.1053/crad.2000.0656
448. Jamtvedt G, Dahm KT, Holm I, Odegaard-Jensen J, Flottorp S. Choice of treatment modalities was not influenced by pain, severity or co-morbidity in patients with knee osteoarthritis. Physiother Res Int. 2010 Mar;15(1):16-23. doi: 10.1002/pri.452
449. Lubbeke A, Katz JN, Perneger TV, Hoffmeyer P. Primary and revision hip arthroplasty: 5-year outcomes and influence of age and comorbidity. J Rheumatol. 2007 Feb;34(2):394-400.
450. Mathers CD, Iburg KM, Begg S. Adjusting for dependent comorbidity in the calculation of healthy life expectancy. Population Health Metrics. 2006;4:4. doi: 10.1186/1478-7954-4-4
451. Mitchell JM, Burkhauser RV, Pincus T. The importance of age, education, and comorbidity in the substantial earnings losses of individuals with symmetric polyarthritis. Arthritis and Rheumatism. 1988;31(3):348-357.
452. Schenk P, Läubli T, Hodler J, Klipstein A. Symptomatology of recurrent low back pain in nursing and administrative professions. European Spine Journal. 2007;16(11):1789-1798. doi: 10.1007/s00586-007-0346-6
453. Sinikallio S, Aalto T, Airaksinen O, Herno A, Kroger H, Savolainen S, et al. Somatic comorbidity and younger age are associated with life dissatisfaction among patients with lumbar spinal stenosis before surgical treatment. Eur Spine J. 2007 Jul;16(7):857-64. doi: 10.1007/s00586-006-0080-5
454. Sterling M, Jull G, Carlsson Y, Crommert L. Are cervical physical outcome measures influenced by the presence of symptomatology? Physiother Res Int. 2002;7(3):113-21.
455. Stollberger C, Winkler-Dworak M, Blazek G, Finsterer J. Cardiologic and neuromuscular co-morbidity influences mortality of patients with left ventricular hypertrabeculation/noncompaction: comparison with the Austrian general population. Acta Cardiol. 2007 Feb;62(1):1-5.
456. Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2009;5(4):355-62.
457. Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. Pain medicine (Malden, Mass.). 2008;9(4):425-32.
458. Arnold BS, Alpers GW, Süss H, Friedel E, Kosmützky G, Geier A, et al. Affective pain modulation in fibromyalgia, somatoform pain disorder, back pain, and healthy controls. European journal of pain (London, England). 2008;12(3):329-38.
459. Bazzichi L, Maser J, Piccinni A, Rucci P, Del Debbio A, Vivarelli L, et al. Quality of life in rheumatoid arthritis: Impact of disability and lifetime depressive spectrum symptomatology. Clinical and Experimental Rheumatology. 2005;23(6):783-788.
460. Brox JI, Reikerås O, Nygaard Ø, Sørensen R, Indahl A, Holm I, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. Pain. 2006;122(1-2):145-55.
461. Hanefeld C, Miebach T, Bulut D, Theodoridis T, Rubenthaler F, Krämer J, et al. [Effects of lumbar spinal nerve analgesia on the cardiovascular system]. Zeitschrift für Orthopädie und ihre Grenzgebiete. 2005;143(1):86-90.
462. Koster A, Bosma H, Kempen GIJM, Van Lenthe FJ, Van Eijk JTM, Mackenbach JP. Socioeconomic inequalities in mobility decline in chronic disease groups (asthma/COPD, heart disease, diabetes mellitus, low back pain): Only a minor role for disease severity and comorbidity. Journal of Epidemiology and Community Health. 2004;58(10):862-869. doi: 10.1136/jech.2003.018317
463. Rupp I, Boshuizen HC, Roorda LD, Dinant HJ, Jacobi CE, van den Bos G. Poor and good health outcomes in rheumatoid arthritis: the role of comorbidity. J Rheumatol. 2006 Aug;33(8):1488-95.
464. Stollberger C, Blazek G, Winkler-Dworak M, Finsterer J. In- and outpatients with noncompaction: differences in cardiac and neuromuscular co-morbidity. Int J Cardiol. 2010 Apr 1;140(1):108-11. doi: 10.1016/j.ijcard.2008.10.041
465. Wylie JD, Bershadsky B, Iannotti JP. The effect of medical comorbidity on self-reported shoulder-specific health related quality of life in patients with shoulder disease. J Shoulder Elbow Surg. 2010 Sep;19(6):823-8. doi: 10.1016/j.jse.2009.11.052
466. Lagana L, Reger SL. A pilot study on perceived stress and PTSD symptomatology in relation to four dimensions of older women's physical health. Aging and Mental Health. 2009;13(6):885-893. doi: 10.1080/13607860903004023
467. Bertrem C, Bruffaerts R, Bonnewyn A, Van Oyen H, Demarest S, Demyttenaere K. Mental and pain comorbidity of chronic somatic disorders in the general population in Belgium. Archives of Public Health. 2006;64(5):199-214.

468. Nguyen LL, Lipsitz SR, Bandyk DF, Clowes AW, Moneta GL, Belkin M, et al. Resource utilization in the treatment of critical limb ischemia: The effect of tissue loss, comorbidities, and graft-related events. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2006;44(5):971-5; discussion 975-6.
469. Tortamano A, Lenzi DC, Haddad AC, Bottino MC, Dominguez GC, Vigorito JW. Low-level laser therapy for pain caused by placement of the first orthodontic archwire: a randomized clinical trial. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. 2009;136(5):662-7.
470. Rabeneck L, Wristers K, Goldstein JL, Eisen G, Dedhiya SD, Burke TA. Reliability, validity, and responsiveness of severity of dyspepsia assessment (SODA) in a randomized clinical trial of a COX-2-specific inhibitor and traditional NSAID therapy. The American journal of gastroenterology. 2002;97(1):32-9.
471. Ang DC, Bair MJ, Damush TM, Wu J, Tu W, Kroenke K. Predictors of pain outcomes in patients with chronic musculoskeletal pain co-morbid with depression: results from a randomized controlled trial. Pain medicine (Malden, Mass.) [Randomized Controlled Trial; Research Support, N.I.H., Extramural]. 2010;11(4):482-91. doi: 10.1111/j.1526-4637.2009.00759.x
472. Beales DJ, Smith AJ, O'Sullivan PB, Straker LM. Low back pain and comorbidity clusters at 17 years of age: A cross-sectional examination of health-related quality of life and specific low back pain impacts. Journal of Adolescent Health. 2012;50(5):509-516. Available from: PsycINFO. doi: 10.1016/j.jadohealth.2011.09.017
473. Bron C, Dommerholt J, Stegenga B, Wensing M, Oostendorp RA. High prevalence of shoulder girdle muscles with myofascial trigger points in patients with shoulder pain. BMC musculoskeletal disorders [Controlled Clinical Trial;]. 2011;12:139. doi: 10.1186/1471-2474-12-139
474. Carbonell-Baeza A, Romero A, Aparicio VA, Ortega FB, Tercedor P, Delgado-Fernández M, et al. Preliminary findings of a 4-month Tai Chi intervention on tenderness, functional capacity, symptomatology, and quality of life in men with fibromyalgia. American Journal of Men's Health. 2011;5(5):421-429. Available from: PsycINFO. doi: 10.1177/1557988311400063
475. Clark F, Jackson J, Carlson M, Chou CP, Cherry BJ, Jordan-Marsh M, et al. Effectiveness of a lifestyle intervention in promoting the well-being of independently living older people: results of the Well Elderly 2 Randomised Controlled Trial. Journal of epidemiology and community health [Randomized Controlled Trial; Research Support, N.I.H., Extramural]. 2012;66(9):782-90. doi: 10.1136/jech.2009.099754
476. Heo M, Allison DB, Faith MS, Zhu S, Fontaine KR. Obesity and Quality of Life: Mediating Effects of Pain and Comorbidities. Obesity. 2003;11(2):209-216.
477. Hoogeboom TJ, den Broeder AA, de Bie RA, van den Ende CH. Longitudinal impact of joint pain comorbidity on quality of life and activity levels in knee osteoarthritis: data from the Osteoarthritis Initiative. Rheumatology (Oxford). 2013 Mar;52(3):543-6. doi: 10.1093/rheumatology/kes314
478. Konnopka A, Heinrich S, Zieger M, Luppa M, Riedel-Heller SG, Meisel HJ, et al. Effects of psychiatric comorbidity on costs in patients undergoing disc surgery: A cross-sectional study. Spine Journal. 2011;11(7):601-609.
479. Konnopka A, Löbner M, Luppa M, Heider D, Heinrich S, Riedel-Heller S, et al. Psychiatric comorbidity as predictor of costs in back pain patients undergoing disc surgery: A longitudinal observational study. BMC Musculoskeletal Disorders. 2012;13:165. doi: 10.1186/1471-2474-13-165
480. Prüfer C, Pereira H, Arezes PM, Neves A, Loureiro M, Soares P, et al. Guimaraes. p. 167-171. [cited 14 February 2013 through 15 February 2013]. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84875513573&partnerID=40&md5=0e83b15a2168769b012ef4496982166b
481. Romero-Zurita A, Carbonell-Baeza A, Aparicio VA, Ruiz JR, Tercedor P, Delgado-Fernandez M. Effectiveness of a tai-chi training and detraining on functional capacity, symptomatology and psychological outcomes in women with fibromyalgia. Evid Based Complement Alternat Med. 2012;2012:614196. doi: 10.1155/2012/614196
482. Salanitro AH, Hovater M, Hearld KR, Roth DL, Sawyer P, Locher JL, et al. Symptom burden predicts hospitalization independent of comorbidity in community-dwelling older adults. J Am Geriatr Soc. 2012 Sep;60(9):1632-7. doi: 10.1111/j.1532-5415.2012.04121.x
483. Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. Annals of the Rheumatic Diseases. 2008;67(9):1310-1316.
484. Smith BN, Shipherd JC, Schuster JL, Vogt DS, King LA, King DW. Posttraumatic stress symptomatology as a mediator of the association between military sexual trauma and post-deployment physical health in women. J Trauma Dissociation. 2011;12(3):275-89. doi: 10.1080/15299732.2011.551508
485. Smith BN, Wang JM, Vogt D, Vickers K, King DW, King LA. Gulf war illness: symptomatology among veterans 10 years after deployment. J Occup Environ Med. 2013 Jan;55(1):104-10. doi: 10.1097/JOM.0b013e318270d709
486. Solomon A, Dobranici L, Kareholt I, Tudose C, Lazarescu M. Comorbidity and the rate of cognitive decline in patients with Alzheimer dementia. Int J Geriatr Psychiatry. 2011 Dec;26(12):1244-51. doi: 10.1002/gps.2670

487. Sperber AD, Akiva S, Leshno M, Halpern Z, Buskila D. Validation of New Symptom-Based Fibromyalgia Criteria for Irritable Bowel Syndrome Co-morbidity Studies. J Neurogastroenterol Motil. 2011 Jan;17(1):67-72. doi: 10.5056/jnm.2011.17.1.67
488. Stengler K, Zieger M, Luppa M, Meisel HJ, Günther L, Meixensberger J, et al. The Impact of Psychiatric Comorbidity on Quality of Life in Patients Undergoing Herniated Disc Surgery. Journal of Neurological Surgery Part A: Central European Neurosugery. 2012;73(1):29-37.
489. Sun YQ, Yang B, Tong SL, Sun J, Zhu YC. Patelloplasty versus traditional total knee arthroplasty for osteoarthritis. Orthopedics [Comparative Study; Randomized Controlled Trial]. 2012;35(3):e343-8. doi: 10.3928/01477447-20120222-14
490. Toll DE, Popovi N, Drinkuth N. The use of MRI diagnostics in orthognathic surgery: prevalence of TMJ pathologies in Angle Class I, II, III patients. Journal of orofacial orthopedics = Fortschritte der Kieferorthopädie : Organ/official journal Deutsche Gesellschaft für Kieferorthopädie [Randomized Controlled Trial]. 2010;71(1):68-80. doi: 10.1007/s00056-010-0903-1
491. Vindigni D, Walker B, Jamison J, Da Costa C, Parkinson L, Blunden S. Low back pain risk factors in a large rural Australian Aboriginal community. An opportunity for managing co-morbidities? Chiropractic & Osteopathy. 2005;13(1):21. doi: 10.1186/1746-1340-13-21
492. Vouilloz A, Deriaz O, Rivier G, Gobelet C, Luthi F. Biopsychosocial complexity is correlated with psychiatric comorbidity but not with perceived pain in complex regional pain syndrome type 1 (algodystrophy) of the knee. Joint Bone Spine. 2011 Mar;78(2):194-9. doi: 10.1016/j.jbspin.2010.07.006
493. Wasan AD, Kong J, Pham LD, Kaptchuk TJ, Edwards R, Gollub RL. The impact of placebo, psychopathology, and expectations on the response to acupuncture needling in patients with chronic low back pain. The journal of pain : official journal of the American Pain Society [Clinical Trial; Randomized Controlled Trial; Research Support, N.I.H., Extramural]. 2010;11(6):555-63. doi: 10.1016/j.jpain.2009.09.013
494. Zieger M, Luppa M, Meisel H, Günther L, Winkler D, Toussaint R, et al. The Impact of Psychiatric Comorbidity on the Return to Work in Patients Undergoing Herniated Disc Surgery. Journal of Occupational Rehabilitation. 2011;21(1):54-65. Available from: c8h. doi: 10.1007/s10926-010-9257-1
495. Becker A, Held H, Redaelli M, Strauch K, Chenot JF, Leonhardt C, et al. Low back pain in primary care: costs of care and prediction of future health care utilization. Spine [Comparative Study; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2010;35(18):1714-20.
496. Gadermann AM, Alonso J, Vilagut G, Zaslavsky AM, Kessler RC. Comorbidity and disease burden in the National Comorbidity Survey Replication (NCS-R). Depression and Anxiety. 2012;29(9):797-806. Available from: PsycINFO. doi: 10.1002/da.21924
497. Goins RT, Pilkerton CS. Comorbidity among older American Indians: The Native Elder Care Study. Journal of Cross-Cultural Gerontology. 2010;25(4):343-354. Available from: PsycINFO. doi: 10.1007/s10823-010-9119-5
498. Scott KM, Von Korff M, Alonso J, Angermeyer MC, Bromet E, Fayyad J, et al. Mental/physical co-morbidity and its relationship with disability: Results from the World Mental Health Surveys. Psychological Medicine. 2009;39(1):33-43. doi: 10.1017/s0033291708003188
499. Blyth FM, Rochat S, Cumming RG, Creasey H, Handelsman DJ, Le Couteur DG, et al. Pain, frailty and comorbidity on older men: The CHAMP study. Pain. 2008 Nov;140(1):224-230. Available from: PsycINFO.
500. Wensing M, Vingerhoets E, Grol R. Functional status, health problems, age and comorbidity in primary care patients. Quality of Life Research. 2001;10(2):141-148. doi: 10.1023/a:1016705615207
501. Annemarie K, Hans B, M KGIJ, J VLF, M VEJT, P MJ. Socioeconomic inequalities in mobility decline in chronic disease groups (asthma/COPD, heart disease, diabetes mellitus, low back pain): only a minor role for disease severity and comorbidity. Journal of Epidemiology & Community Health. 2004;58(10):862-9.
502. Forman-Hoffman VL, Carney CP, Sampson TR, Peloso PM, Woolson RF, Black DW, et al. Mental health comorbidity patterns and impact on quality of life among veterans serving during the first Gulf War. Qual Life Res. 2005 Dec;14(10):2303-14. doi: 10.1007/s11136-005-6540-2
503. Omura Y, Losco BM, Omura AK, Takeshige C, Hisamitsu T, Shimotsuura Y. Common factors contributing to intractable pain and medical problems with insufficient drug uptake in areas to be treated, and their pathogenesis and treatment: Part I. Combined use of medication with acupuncture, (+) Qi gong energy-stored material, soft laser or electrical stimulation. Acupuncture & electro-therapeutics research. 1992;17(2):107-48.
504. Herbert R, Dropkin J, Warren N, Sivin D, Doucette J, Kellogg L, et al. Impact of a joint labor-management ergonomics program on upper extremity musculoskeletal symptoms among garment workers 14. Applied ergonomics. 2001;32(5):453-60. doi: 10.1016/S0003-6870(01)00024-2
505. Menzies D, Popa J, Hanley JA, Rand T, Milton DK. Effect of ultraviolet germicidal lights installed in office ventilation systems on workers' health and wellbeing: Double-blind multiple crossover trial. Lancet. 2003;362(9398):1785-91. doi: 10.1016/S0140-6736%2803%2914897-0
506. Lim AYN, Doherty M. What of guidelines for osteoarthritis? International journal of rheumatic diseases. 2011;14(2):136-44. doi: 10.1111/j.1756-185X.2011.01609.x
507. Poddubnyy D, Vahldiek J, Spiller I, Buss B, Listing J, Rudwaleit M, et al. Evaluation of 2 screening

strategies for early identification of patients with axial spondyloarthritis in primary care. Journal of rheumatology. 2011;38(11):2452-60. doi: 10.3899/jrheum.110070
508. Bruehl S, Liu X, Burns JW, Chont M, Jamison RN. Associations between daily chronic pain intensity, daily anger expression, and trait anger expressiveness: an ecological momentary assessment study. Pain. 2012;153(12):2352-8. doi: 10.1016/j.pain.2012.08.001
509. Venmans A, Klazen CA, Lohle PN, Mali WP, Rooij WJ. Natural history of pain in patients with conservatively treated osteoporotic vertebral compression fractures: results from VERTOS II. AJNR. American journal of neuroradiology. 2012;33(3):519-21. doi: 10.3174/ajnr.A2817
510. Yokoyama K, Kawanishi M, Yamada M, Tanaka H, Ito Y, Hirano M, et al. Comparative study of percutaneous vertebral body perforation and vertebroplasty for the treatment of painful vertebral compression fractures. AJNR. American journal of neuroradiology. 2012;33(4):685-9. doi: 10.3174/ajnr.A2847
511. Asay JL, Boyer KA, Andriacchi TP. Repeatability of gait analysis for measuring knee osteoarthritis pain in patients with severe chronic pain. Journal of orthopaedic research. 2013;31(7):1007-12. doi: 10.1002/jor.22228
512. Chelly JE, Singla SK, Melson TI, Lacouture PG, Paadre S, Carr DB. Safety of a novel parenteral formulation of diclofenac after major orthopedic or abdominal/pelvic surgery in a population including anticoagulated, elderly or renally insufficient patients: an open-label, multiday, repeated dose clinical trial. Pain medicine (Malden, Mass.). 2013;15(5):749-61. doi: 10.1111/pme.12076
513. Comstock BA, Sitlani CM, Jarvik JG, Heagerty PJ, Turner JA, Kallmes DF. Investigational vertebroplasty safety and efficacy trial (INVEST): patient-reported outcomes through 1 year. Radiology. 2013;269(1):224-31. doi: 10.1148/radiol.13120821
514. Dhingra L, Masson C, Perlman DC, Seewald RM, Katz J, McKnight C, et al. Epidemiology of pain among outpatients in methadone maintenance treatment programs. Drug and alcohol dependence. 2013;128(1-2):161-5. doi: 10.1016/j.drugalcdep.2012.08.003
515. Hermsen LA, Leone SS, Smalbrugge M, Knol DL, van der Horst HE, Dekker J. Exploring the aggregation of four functional measures in a population of older adults with joint pain and comorbidity. BMC Geriatr. 2013;13:119. doi: 10.1186/1471-2318-13-119
516. Leonard MT, Chatkoff DK, Gallaway M. Association between pain catastrophizing, spouse responses to pain, and blood pressure in chronic pain patients: a pathway to potential comorbidity. Int J Behav Med. 2013 Dec;20(4):590-8. doi: 10.1007/s12529-012-9262-1
517. Shadick NA, Sowell NF, Frits ML, Hoffman SM, Hartz SA, Booth FD, et al. A randomized controlled trial of an internal family systems-based psychotherapeutic intervention on outcomes in rheumatoid arthritis: A proof-of-concept study. Journal of rheumatology. 2013;40(11):1831-41. doi: 10.3899/jrheum.121465
518. Weiss J, Quante S, Xue F, Muche R, Reuss-Borst M. Effectiveness and acceptance of acupuncture in patients with chronic low back pain: Results of a prospective, randomized, controlled trial. Journal of alternative and complementary medicine (New York, N.Y.). 2013;19(12):935-41. doi: 10.1089/acm.2012.0338
519. Cooper C. The lifecourse epidemiology of musculoskeletal ageing. Osteoporosis international. 2014;25(S2):S101-s102. doi: 10.1007/s00198-014-2637-1
520. Mannion AF, Fekete TF, Porchet F, Haschtmann D, Jeszenszky D, Kleinstuck FS. The influence of comorbidity on the risks and benefits of spine surgery for degenerative lumbar disorders. Eur Spine J. 2014 Apr;23 Suppl 1:S66-71. doi: 10.1007/s00586-014-3189-y
521. Rodger KTM, Greasley-Adams C, Hodge Z, Reynish E. Expert opinion on the management of pain in elderly patients with cognitive impairment: A survey of consultant geriatricians with specialist interest. Alzheimer's & dementia. 2014;10(4):P858. doi: 10.1016/j.jalz.2014.05.1705
522. Short TG, Leslie K, Campbell D, Chan MT, Corcoran T, O'Loughlin E, et al. A pilot study for a prospective, randomized, double-blind trial of the influence of anesthetic depth on long-term outcome. Anesthesia and analgesia. 2014;118(5):981-6. doi: 10.1213/ANE.0000000000000209
523. Ramond-Roquin A, Pecquenard F, Schers H, Van Weel C, Oskam S, Van Boven K. Psychosocial, musculoskeletal and somatoform comorbidity in patients with chronic low back pain: original results from the Dutch Transition Project. Fam Pract. 2015 Apr 24;32(3):297-304. doi: 10.1093/fampra/cmv027
524. Bair MJ, Poleshuck EL, Wu J, Krebs EK, Damush TM, Tu W, et al. Anxiety but not social stressors predict 12-month depression and pain severity. The Clinical journal of pain. 2013;29(2):95-101. doi: 10.1097/AJP.0b013e3182652ee9
525. Necas M. Musculoskeletal symptomatology and repetitive strain injuries in diagnostic medical sonographers: A pilot study in Washington and Oregon. Journal of Diagnostic Medical Sonography. 1996;12(6):266-273.
526. Merikangas KR, Ames M, Cui L, Stang PE, Ustun TB, Von Korff M, et al. The impact of comorbidity of mental and physical conditions on role disability in the US adult household population. Arch Gen Psychiatry. 2007 Oct;64(10):1180-8. doi: 10.1001/archpsyc.64.10.1180
527. Careddu P, Scotti A. Controlled, double-blind, multicenter clinical trial of iron protein succinylate in the treatment of iron deficiency in children. International journal of clinical pharmacology, therapy, and toxicology. 1993;31(4):157-69.

528. Creed F, Guthrie E, Ratcliffe J, Fernandes L, Rigby C, Tomenson B, et al. Does psychological treatment help only those patients with severe irritable bowel syndrome who also have a concurrent psychiatric disorder? The Australian and New Zealand journal of psychiatry. 2005;39(9):807-15.
529. De Jong WH, Kallewaard M, Goldhoorn CA, Verhoef CM, Bijlsma JW, Schouten JS, et al. Long-term exposure to silicone breast implants does not induce antipolymer antibodies. Biomaterials. 2004;25(6):1095-103.
530. Eckhardt SG, De Porre P, Smith D, Maurel J, Steward WP, Bouche O, et al. Patient-reported outcomes as a component of the primary endpoint in a double-blind, placebo-controlled trial in advanced pancreatic cancer. Journal of pain and symptom management. 2009;37(2):135-43.
531. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: a randomized controlled trial. Archives of general psychiatry. 1999;56(10):932-9.
532. Gillberg C, Melander H, von Knorring AL, Janols LO, Thernlund G, Hägglöf B, et al. Long-term stimulant treatment of children with attention-deficit hyperactivity disorder symptoms. A randomized, double-blind, placebo-controlled trial. Archives of general psychiatry. 1997;54(9):857-64.
533. Han C, Masand PS, Krulewicz S, Peindl K, Mannelli P, Varia IM, et al. Childhood abuse and treatment response in patients with irritable bowel syndrome: a post-hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release. Journal of clinical pharmacy and therapeutics. 2009;34(1):79-88.
534. Levenson JL, Hamer RM, Rossiter LF. A randomized controlled study of psychiatric consultation guided by screening in general medical inpatients. The American journal of psychiatry. 1992;149(5):631-7.
535. Liguori L. Iron protein succinylate in the treatment of iron deficiency: controlled, double-blind, multicenter clinical trial on over 1,000 patients. International journal of clinical pharmacology, therapy, and toxicology. 1993;31(3):103-23.
536. Makin AJ, Chung NA, Silverman SH, Lip GY. Thrombogenesis and endothelial damage/dysfunction in peripheral artery disease. Relationship to ethnicity and disease severity. Thrombosis research. 2003;111(4-5):221-6.
537. Man SY, Wong EM, Ng YC, Lau PF, Chan MS, Lopez V, et al. Cost-consequence analysis comparing 2-octyl cyanoacrylate tissue adhesive and suture for closure of simple lacerations: a randomized controlled trial. Annals of emergency medicine. 2009;53(2):189-97.
538. Martinsons A, Narbuts Z, Brunenieks I, Pavars M, Lebedkovs S, Gardovskis J. A comparison of quality of life and postoperative results from combined PPH and conventional haemorrhoidectomy in different cases of haemorrhoidal disease. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2007;9(5):423-9.
539. Pautex S, Michon A, Guedira M, Emond H, Le Lous P, Samaras D, et al. Pain in severe dementia: self-assessment or observational scales? Journal of the American Geriatrics Society. 2006;54(7):1040-5.
540. Peters KM, Diokno AC, Steinert BW, Gonzalez JA. The efficacy of intravesical bacillus Calmette-Guerin in the treatment of interstitial cystitis: long-term followup. The Journal of urology. 1998;159(5):1483-6; discussion 1486-7.
541. Seftel AD, Wilson SK, Knapp PM, Shin J, Wang WC, Ahuja S. The efficacy and safety of tadalafil in United States and Puerto Rican men with erectile dysfunction. The Journal of urology. 2004;172(2):652-7.
542. Woods K, Douketis JD, Schnurr T, Kinnon K, Powers P, Crowther MA. Patient preferences for capillary vs. venous INR determination in an anticoagulation clinic: a randomized controlled trial. Thrombosis research. 2004;114(3):161-5.
543. Woolridge E, Barton S, Samuel J, Osorio J, Dougherty A, Holdcroft A. Cannabis use in HIV for pain and other medical symptoms. Journal of pain and symptom management. 2005;29(4):358-67.
544. Wustrow TP. [Naturopathic therapy for acute otitis media. An alternative to the primary use of antibiotics]. Hno. 2005;53(8):728-34.
545. Xie ZB, Jiang YL. [Effects of psychological interventions on emotion and quality of life of elderly patients with benign prostatic hypertrophy]. Zhongguo Linchuang Kangfu. 2005;9(24):44-6.
546. Yun YH, Wang XS, Lee JS, Roh JW, Lee CG, Lee WS, et al. Validation study of the korean version of the brief fatigue inventory. Journal of pain and symptom management. 2005;29(2):165-72.
547. Haack M, Mullington JM. Sustained sleep restriction reduces emotional and physical well-being. Pain. 2005;119(1-3):56-64.
548. Lagana L, Chen X, Koopman C, Classen C, Kimerling R, Spiegel D. Depressive symptomatology in relation to emotional control and chronic pain in persons who are HIV positive. Rehabilitation Psychology. 2002 11;47(4):402-414.
549. Williams JW, Kerber CA, Mulrow CD, Medina A, Aguilar C. Depressive disorders in primary care: prevalence, functional disability, and identification. Journal of general internal medicine. 1995;10(1):7-12.
550. Réthelyi JM, Berghammer R, Kopp MS. Comorbidity of pain-associated disability and depressive symptoms in connection with sociodemographic variables: Results from a cross-sectional epidemiological survey in Hungary. Pain. 2001;93(2):115-121. doi: 10.1016/s0304-3959(01)00301-3
551. No antibiotics necessary for lower respiratory infection. South African Family Practice. 2005;47(7):10.

552. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurologica Scandinavica. 2004;110(4):207-220. doi: 10.1111/j.1600-0404.2004.00324.x
553. Gonzalez SA, Talal AH. Hepatitis C virus in human immunodeficiency virus-infected individuals: An emerging comorbidity with significant implications. Seminars in Liver Disease. 2003;23(2):149-166. doi: 10.1055/s-2003-39946
554. Guadagnino V, Trotta MP, Carioti J, Caroleo B, Antinori A. Does depression symptomatology affect medication compliance during the first weeks of anti-HCV therapy in intravenous drug users? Digestive and Liver Disease. 2006;38(2):119-124. doi: 10.1016/j.dld.2005.10.008
555. Holmstrand C, Engström G, Träskman-Bendz L. Disentangling dysthymia from major depressive disorder in suicide attempters' suicidality, comorbidity and symptomatology. Nordic Journal of Psychiatry. 2008;62(1):25-31. doi: 10.1080/08039480801960164
556. Korenkov M, Shah S, Sauerland S, Duenschede F, Junginger T. Impact of laparoscopic adjustable gastric banding on obesity co-morbidities in the medium- and long-term. Obesity Surgery. 2007;17(5):679-683. doi: 10.1007/s11695-007-9118-y
557. Schultz HY. Society for investigative dermatology skin disease Co-Morbidities Project Launch Conference Proceedings. Journal of Investigative Dermatology. 2009;129(3):525-528. doi: 10.1038/jid.2008.417
558. Sullivan EV, Rosenbloom MJ, Pfefferbaum A. Balance and Gait Deficits in Schizophrenia Compounded by the Comorbidity of Alcoholism. American Journal of Psychiatry. 2004;161(4):751-755. doi: 10.1176/appi.ajp.161.4.751
559. Wang SJ, Liu HC, Fuh JL, Liu CY, Wang PN, Lu SR. Comorbidity of headaches and depression in the elderly. Pain. 1999;82(3):239-243. doi: 10.1016/s0304-3959(99)00057-3
560. Viner MW, Waite J, Thienhaus OJ. Comorbidity and the need for physical examinations among patients seen in the psychiatric emergency service. Psychiatric Services. 1996;47(9):947-948.
561. Wandell PE, Brorsson B, Aberg H. Quality of life in relation to comorbidity among diabetic patients followed for three years in swedish primary health care. Diabetes and Metabolism. 1999;25(5):424-428.
562. Kopp MS, Falger PR, Appels A, Szedmak S. Depressive symptomatology and vital exhaustion are differentially related to behavioral risk factors for coronary artery disease. Psychosom Med. 1998 Nov-Dec;60(6):752-8.
563. Lagana L, Reger SL. A pilot study on perceived stress and PTSD symptomatology in relation to four dimensions of older women's physical health. Aging Ment Health. 2010 May;14(4):396-404. doi: 10.1080/13607860903046578
564. Lau CP, Rushby J, Leigh-Jones M, Tam CY, Poloniecki J, Ingram A, et al. Symptomatology and quality of life in patients with rate-responsive pacemakers: a double-blind, randomized, crossover study. Clin Cardiol. 1989 Sep;12(9):505-12.
565. Lindgren TG, Fukuoka Y, Rankin SH, Cooper BA, Carroll D, Munn YL. Cluster analysis of elderly cardiac patients' prehospital symptomatology. Nursing Research. 2008;57(1):14-23. doi: 10.1097/01.NNR.0000280654.50642.1a
566. Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. Sleep. 2007;30(2):213-218.
567. van Manen JG, Bindels PJ, Dekker FW, Bottema BJ, van der Zee JS, Ijzermans CJ, et al. The influence of COPD on health-related quality of life independent of the influence of comorbidity. J Clin Epidemiol. 2003 Dec;56(12):1177-84.
568. Côté P, Cassidy JD, Carroll L. Is a lifetime history of neck injury in a traffic collision associated with prevalent neck pain, headache and depressive symptomatology? Accident Analysis and Prevention. 2000;32(2):151-159. doi: 10.1016/s0001-4575(99)00117-7
569. De Vecchis R, Zarrelli V, Imperatore A, Vergara G, Scafuro F, Cimmino G, et al. Differences in the symptomatology of paroxysmal supraventricular tachycardias in relation to the different sites of localization of the arrhythmic reentry circuit. Clinical picture, semiologic and genetic aspects. Diversità di sintomatologia nelle tachicardie parossistiche sopraventricolari (TPSR) correlata alla differente localizzazione del circuito aritmico di rientro. Analisi del quadro clinico e considerazioni semeiogenetiche. 1993;41(1-2):1-16.
570. Enochsson L, Hellberg A, Rudberg C, Feny?G, Gudbjartson T, Kullman E, et al. Laparoscopic vs open appendectomy in overweight patients. Surgical endoscopy. 2001;15(4):387-92.
571. Essau CA, Conradt J, Petermann F. Prevalence, comorbidity and psychosocial impairment of somatoform disorders in adolescents. Psychology, Health and Medicine. 1999;4(2):169-180. doi: 10.1080/135485099106306
572. Ferrada-Noli M, Asberg M, Ormstad K, Lundin T, Sundbom E. Suicidal behavior after severe trauma. Part 1: PTSD diagnoses, psychiatric comorbidity, and assessments of suicidal behavior. Journal of Traumatic Stress. 1998;11(1):103-112. doi: 10.1023/a:1024461216994
573. Fluge G, Olesen HV, Gilljam M, Meyer P, Pressler T, Storrösten OT, et al. Co-morbidity of cystic fibrosis and celiac disease in Scandinavian cystic fibrosis patients. Journal of Cystic Fibrosis. 2009;8(3):198-202. doi: 10.1016/j.jcf.2009.02.002
574. Gaeta G, Massari A, Scala R, De Rosa V, Boccalatte M, Bolletti Censi M. Relationship between symptomatology of acute ischemic heart disease and glucose metabolism balance. Rapporti tra sintomatologia

della cardiopatia ischemica acuta e controllo glicometabolico. 1994;42(7-8):333-338.
575. Kauer-Sant'Anna M, Frey BN, Andreazza AC, Ceres 茅 r KM, Gazalle FK, Tramontina J, et al. Anxiety comorbidity and quality of life in bipolar disorder patients. The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie. 2007 Mar;52(3):175-181. Available from: PsycINFO.
576. Gaitatzis A, Carroll K, Majeed A, Sander JW. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia. 2004;45(12):1613-1622. doi: 10.1111/j.0013-9580.2004.17504.x
577. Moore AA, Giuli L, Gould R, Hu P, Zhou K, Reuben D, et al. Alcohol use, comorbidity, and mortality. Journal of the American Geriatrics Society. 2006;54(5):757-762. doi: 10.1111/j.1532-5415.2006.00728.x
578. Paul SB, Gulati MS, Sreenivas V, Madan K, Gupta AK, Mukhopadhyay S, et al. Evaluating patients with cirrhosis for hepatocellular carcinoma: Value of clinical symptomatology, imaging and alpha-fetoprotein. Oncology. 2007;72(SUPPL. 1):117-123. doi: 10.1159/000111717
579. Suija K, Kalda R, Maaroos HI. Patients with depressive disorder, their co-morbidity, visiting rate and disability in relation to self-evaluation of physical and mental health: A cross-sectional study in family practice. BMC Family Practice. 2009;10. doi: 10.1186/1471-2296-10-38
580. Blum N, Franklin J, Hansel R, McCormick B, St. John D, Pfohl B, et al. Relationship of age to symptom severity, psychiatric comorbidity and health care utilization in persons with borderline personality disorder. Personality and Mental Health. 2008;2(1):25-34. Available from: PsycINFO. doi: 10.1002/pmh.26
581. Breckan RK, Asfeldt AM, Straume B, Florholmen J, Paulssen EJ. Prevalence, comorbidity, and risk factors for functional bowel symptoms: a population-based survey in Northern Norway. Scand J Gastroenterol. 2012 Nov;47(11):1274-82. doi: 10.3109/00365521.2012.688215
582. Caughey GE, Roughead EE, Shakib S, McDermott RA, Vitry AI, Gilbert AL. Comorbidity of chronic disease and potential treatment conflicts in older people dispensed antidepressants. Age Ageing. 2010 Jul;39(4):488-94. doi: 10.1093/ageing/afq055
583. Darcy JM, Grzywacz JG, Stephens RL, Leng I, Clinch CR, Arcury TA. Maternal depressive symptomatology: 16-month follow-up of infant and maternal health-related quality of life. J Am Board Fam Med. 2011 May-Jun;24(3):249-57. doi: 10.3122/jabfm.2011.03.100201
584. Domínguez-Cabello E, Martín-Rodriguez A, Pérez-San-Gregorio MA, Pérez-Bernal J. Influence of relatives' anxious symptomatology on the quality of life of pretransplant hepatic patients. Transplantation Proceedings. 2010;42(8):2964-2965.
585. Fagerström C, Hellström A. Sleep complaints and their association with comorbidity and health-related quality of life in an older population in Sweden. Aging and Mental Health. 2011;15(2):204-213.
586. Given CW, Bradley C, You M, Sikorskii A, Given B. Costs of novel symptom management interventions and their impact on hospitalizations. Journal of pain and symptom management [Randomized Controlled Trial; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't]. 2010;39(4):663-72. doi: 10.1016/j.jpainsymman.2009.07.014
587. Kurtz ME, Kurtz JC, Given CW, Given B. A Randomized, Controlled Trial of a Patient/Caregiver Symptom Control Intervention: Effects on Depressive Symptomatology of Caregivers of Cancer Patients. Journal of Pain and Symptom Management. 2005;30(2):112-122. Available from: PsycINFO. doi: 10.1016/j.jpainsymman.2005.02.008
588. Marcus GM, Chan DW, Redberg RF. Recollection of pain due to inappropriate versus appropriate implantable cardioverter-defibrillator shocks. Pacing and clinical electrophysiology : PACE [Controlled Clinical Trial; Research Support, N.I.H., Extramural]. 2011;34(3):348-53. doi: 10.1111/j.1540-8159.2010.02971.x
589. Oğurlu N, Küçük M, Aksu H. Influence of employment status on menopausal symptoms. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics [Randomized Controlled Trial]. 2011;112(3):204-7. doi: 10.1016/j.ijgo.2010.10.010
590. Pereiro C, Pino C, Flórez G, Arrojo M, Becoña E. Psychiatric Comorbidity in Patients from the Addictive Disorders Assistance Units of Galicia: The COPSIAD Study. PLoS ONE. 2013;8(6):e66451. doi: 10.1371/journal.pone.0066451
591. Phifer J, Skelton K, Weiss T, Schwartz AC, Wingo A, Gillespie CF, et al. Pain symptomatology and pain medication use in civilian PTSD. Pain. 2011;152(10):2233-2240. Available from: PsycINFO. doi: 10.1016/j.pain.2011.04.019
592. Picco PP, D'Alessandro M, Leoni M, Doglio M, Martini A. Primary red ear syndrome associated with cochleo-vestibular symptomatology: A paediatric case report. Cephalalgia. 2013 Jun 25;33(15):1277-80. doi: 10.1177/0333102413493527
593. Trull TJ, Jahng S, Tomko RL, Wood PK, Sher KJ. Revised NESARC personality disorder diagnoses: Gender, prevalence, and comorbidity with substance dependence disorders. Journal of Personality Disorders. 2010;24(4):412-426. Available from: PsycINFO. doi: 10.1521/pedi.2010.24.4.412
594. Zirke N, Seydel C, Szczepek AJ, Olze H, Haupt H, Mazurek B. Psychological comorbidity in patients with chronic tinnitus: Analysis and comparison with chronic pain, asthma or atopic dermatitis patients. Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care & Rehabilitation. 2013;22(2):263-272. Available from: PsycINFO. doi: 10.1007/s11136-012-0156-0

595. Cicero TJ, Surratt HL, Kurtz S, Ellis MS, Inciardi JA. Patterns of prescription opioid abuse and comorbidity in an aging treatment population. Journal of Substance Abuse Treatment. 2012;42(1):87-94. Available from: PsycINFO. doi: 10.1016/j.jsat.2011.07.003
596. Rosenberger PH, Henderson KE, Grilo CM. Psychiatric disorder comorbidity and association with eating disorders in bariatric surgery patients: A cross-sectional study using structured interview-based diagnosis. Journal of Clinical Psychiatry. 2006;67(7):1080-1085. Available from: PsycINFO. doi: 10.4088/JCP.v67n0710
597. D'Antono B, Goldfarb M, Solomon C, Sturmer M, Becker G, Essebag V, et al. Psychological impact of surveillance in patients with a defibrillator lead under advisory: a prospective evaluation. Pacing and clinical electrophysiology : PACE. 2013;36(2):221-30. doi: 10.1111/pace.12040
598. Denoya PI, Fakhoury M, Chang K, Fakhoury J, Bergamaschi R. Dearterialization with mucopexy versus haemorrhoidectomy for grade III or IV haemorrhoids: Short-term results of a double-blind randomized controlled trial. Colorectal disease. 2013;15(10):1281-8. doi: 10.1111/codi.12303
599. Garg S, Songara P, Sherwal BL, Agarwal S, Rakshit P, Kumar S. Fungal rhinosinusitis in Delhi-National Capital Region. Clinical Rhinology. 2013;6(1):28-31. doi: 10.5005/jp-journals-10013-1144
600. Macesic N, Kotsimbos TC, Kelly P, Cheng AC. Hospital-acquired influenza in an Australian sentinel surveillance system. Medical journal of Australia. 2013;198(7):370-2. doi: 10.5694/mja12.11687
601. Nielsen S, Hillhouse M, Thomas C, Hasson A, Ling W. A comparison of buprenorphine taper outcomes between prescription opioid and heroin users. Journal of addiction medicine. 2013;7(1):33-8. doi: 10.1097/ADM.0b013e318277e92e
602. Pinzon LC, Claus M, Perrar KM, Zepf KI, Letzel S, Weber M. Dying with dementia: symptom burden, quality of care, and place of death. Deutsches Ärzteblatt international. 2013;110(12):195-202. doi: 10.3238/arztebl.2013.0195
603. Sansone RA, Watts DA, Wiederman MW. Pain and pain catastrophizing among internal medicine outpatients with borderline personality symptomatology: a cross-sectional self-report survey. Prim Care Companion CNS Disord. 2013;15(5):pii: PCC.13m01536. doi: 10.4088/PCC.13m01536
604. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. International journal of obesity (2005). 2013;37(11):1443-51. doi: 10.1038/ijo.2013.120
605. Dubeau CE, Kraus SR, Griebling TL, Newman DK, Wyman JF, Johnson IT, et al. Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: A double-blind, placebo controlled trial. Journal of urology. 2014;191(2):395-404. doi: 10.1016/j.juro.2013.08.027
606. Mohanty S, Santangeli P, Mohanty P, Biase LD, Holcomb S, Trivedi C, et al. Catheter ablation of asymptomatic longstanding persistent atrial fibrillation: Impact on quality of life, exercise performance, arrhythmia perception, and arrhythmia-free survival. Journal of cardiovascular electrophysiology. 2014;24(10):1057-64. doi: 10.1111/jce.12467
607. Paulus GF, Verlaan T, Mathus-Vliegen EMH, Veldhuyzen E, Conchillo JM, Fockens P, et al. Endoscopic gastric volume reduction with a novel articulating plication device is safe and effective in the treatment of obesity. Obesity surgery. 2014;24(7):1000. doi: 10.1007/s11695-014-1265-3
608. Ramtvedt BE, Aabech HS, Sundet K. Minimizing adverse events while maintaining clinical improvement in a pediatric attention-deficit/hyperactivity disorder crossover trial with dextroamphetamine and methylphenidate. Journal of child and adolescent psychopharmacology. 2014;24(3):130-9. doi: 10.1089/cap.2013.0114
609. Tazegul Pekin A, Secilmis Kerimoglu O, Kebapcilar AG, Yilmaz SA, Benzer N, Celik C. Depressive symptomatology and quality of life assessment among women using the levonorgestrel-releasing intrauterine system: an observational study. Arch Gynecol Obstet. 2014 Sep;290(3):507-11. doi: 10.1007/s00404-014-3237-1
610. Wagg A, Cardozo L, Nitti VW, Castro-Diaz D, Auerbach S, Blauwet MB, et al. The efficacy and tolerability of the beta3-adrenoceptor agonist mirabegron for the treatment of symptoms of overactive bladder in older patients. Age and ageing. 2014;43(5):666-75. doi: 10.1093/ageing/afu017
611. Gilchrist PT, McGovern GE, Bekkouche N, Bacon SL, Ditto B. The vasovagal response during confrontation with blood-injury-injection stimuli: The role of perceived control. Journal of anxiety disorders. 2015;31:43-8. doi: 10.1016/j.janxdis.2015.01.009
612. Pérez-San-Gregorio MA, Martín-Rodríguez A, Fernández-Jiménez E, Pérez-Bernal J, Gómez-Bravo MA. Influence of acute cellular rejection and depressive symptomatology on liver transplant recipients' quality of life. Transplantation Proceedings. 2015;47(1):100-103. Available from: Scopus. doi: 10.1016/j.transproceed.2014.11.010
613. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review (Provisional abstract). Journal of Pain and Symptom Management. 2004;28(2):140-175.
614. Escobar JI, Swartz M, Rubio-Stipec M, Manu P. Medically unexplained symptoms: Distribution, risk factors, and comorbidity. In: Kirmayer LJ, Robbins JM, editors. Current concepts of somatization: Research and clinical perspectives; 1991 p.63-78. Available from: PsycINFO
615. Breslau N, Rasmussen BK. The impact of migraine: Epidemiology, risk factors, and co-morbidities.

Neurology. 2001;56(6 SUPPL. 1):S4-12. doi: 10.1212/WNL.56.suppl_1.S4
616. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in iflammatory bowel disease: A review of comorbidity and management. Inflammatory Bowel Diseases. 2009;15(7):1105-1118. doi: 10.1002/ibd.20873
617. Krishnan KRR, Delong M, Kraemer H, Carney R, Spiegel D, Gordon C, et al. Comorbidity of depression with other medical diseases in the elderly. Biological Psychiatry. 2002;52(6):559-588. doi: 10.1016/s0006-3223(02)01472-5
618. Mannelli P, Pae CU. Medical comorbidity and alcohol dependence. Current Psychiatry Reports. 2007;9(3):217-224. doi: 10.1007/s11920-007-0022-x
619. Martinez-Gonzalez D, Obermeyer WH, Benca RM. Comorbidity of insomnia with medical and psychiatric disorders. Economics of Neuroscience. 2001;3(9):48-57.
620. Mazza M, Marano G. Current understanding of comorbidity in anxiety disorders: An integrative approach. Minerva Psichiatrica. 2009;50(3):231-263.
621. McIntyre RS, Nguyen HT, Soczynska JK, Lourenco MTC, Woldeyohannes HO, Konarski JZ. Medical and substance-related comorbidity in bipolar disorder: Translational research and treatment opportunities. Dialogues in Clinical Neuroscience. 2008;10(2):203-213.
622. Peacock J, Benca RM. Narcolepsy: Clinical features, co-morbidities & treatment. Indian Journal of Medical Research. 2010;131(2):338-349.
623. Peric H, Fraser IS. The symptomatology of adenomyosis. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2006;20(4):547-555. doi: 10.1016/j.bpobgyn.2006.01.006
624. Sheftell FD, Atlas SJ. Migraine and psychiatric comorbidity: From theory and hypotheses to clinical application. Headache. 2002;42(9):934-944. doi: 10.1046/j.1526-4610.2002.02217.x
625. Von Roenn JH, Paice JA. Control of common, non-pain cancer symptoms. Seminars in Oncology. 2005;32(2):200-210. doi: 10.1053/j.seminoncol.2004.11.019
626. Wittchen HU, Lieb R, Wunderlich U, Schuster P. Comorbidity in primary care: Presentation and consequences. Journal of Clinical Psychiatry. 1999;60(SUPPL. 7):29-38.
627. Arnold LM. Management of psychiatric comorbidity in fibromyalgia. Curr Psychiatry Rep. 2006 Jun;8(3):241-5.
628. Athanasos P. Pain: the new co-morbidity. Aust Nurs J. 2007 Nov;15(5):41.
629. Cady R, Farmer K, Dexter JK, Schreiber C. Cosensitization of pain and psychiatric comorbidity in chronic daily headache. Curr Pain Headache Rep. 2005 Feb;9(1):47-52.
630. Campo JV, Gilchrist RH. Psychiatric comorbidity and functional abdominal pain. Pediatr Ann. 2009 May;38(5):283-7.
631. Fishbain DA. Approaches to treatment decisions for psychiatric comorbidity in the management of the chronic pain patient. Medical Clinics of North America. 1999;83(3):737-760. doi: 10.1016/s0025-7125(05)70132-2
632. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psychiatry. 2009 Aug;70(8):1078-90. doi: 10.4088/JCP.08r04505
633. Gureje O. Comorbidity of pain and anxiety disorders. Curr Psychiatry Rep. 2008 Aug;10(4):318-22.
634. Krueger RF, Tackett JL, Markon KE. Structural models of comorbidity among common mental disorders: connections to chronic pain. Adv Psychosom Med. 2004;25:63-77.
635. Liedl A, Knaevelsrud C. [PTSD and chronic pain: development, maintenance and comorbidity--a review]. Schmerz. 2008 Dec;22(6):644-51. doi: 10.1007/s00482-008-0714-0
636. Mauser-Bunschoten EP, Fransen Van De Putte DE, Schutgens RE. Co-morbidity in the ageing haemophilia patient: the down side of increased life expectancy. Haemophilia. 2009 Jul;15(4):853-63. doi: 10.1111/j.1365-2516.2009.01987.x
637. Nappi G, Costa A, Tassorelli C, Santorelli FM. Migraine as a complex disease: heterogeneity, comorbidity and genotype-phenotype interactions. Funct Neurol. 2000 Apr-Jun;15(2):87-93.
638. Scher AI, Bigal ME, Lipton RB. Comorbidity of migraine. Curr Opin Neurol. 2005 Jun;18(3):305-10.
639. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology. 2002 Apr;122(4):1140-56.
640. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and Pain Comorbidity: A Literature Review. Archives of Internal Medicine. 2003;163(20):2433-2445. doi: 10.1001/archinte.163.20.2433
641. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors: a structured evidence-based review (Structured abstract). Pain Medicine. 2008;9(4):444-459.
642. Hestbaek L, Leboeuf-Yde C, Manniche C. Is low back pain part of a general health pattern or is it a separate and distinctive entity? A critical literature review of comorbidity with low back pain. Journal of Manipulative and Physiological Therapeutics. 2003;26(4):243-252. doi: 10.1016/s0161-4754(03)00003-4
643. Kulich RJ, Mencher P, Bertrand C, Maciewicz R. Comorbidity of post-traumatic stress disorder and chronic pain: implications for clinical and forensic assessment. Current review of pain. 2000;4(1):36-48.
644. Meana M. The meeting of pain and depression: Comorbidity in women. Canadian Journal of Psychiatry.

1998;43(9):893-899.
645. Zaubler TS, Katon W. Panic disorder and medical comorbidity: A review of the medical and psychiatric literature. Bulletin of the Menninger Clinic. 1996;60(2 SUPPL.):A12-38.
646. Kroenke K. Patients presenting with somatic complaints: Epidemiology, psychiatric co-morbidity and management. International Journal of Methods in Psychiatric Research. 2003;12(1):34-43. doi: 10.1002/mpr.140
647. Asmundson GJG, Katz J. Understanding pain and posttraumatic stress disorder comorbidity: Do pathological responses to trauma alter the perception of pain? Pain. 2008;138(2):247-249. doi: 10.1016/j.pain.2008.06.020
648. Beck JG, Clapp JD. A different kind of co-morbidity: Understanding posttraumatic stress disorder and chronic pain. Psychol Trauma. 2011 Jun;3(2):101-108. doi: 10.1037/a0021263
649. Bejjani C, Kunik ME. Psychological co-morbidities of dementia. In: Psychological co-morbidities of physical illness: A behavioral medicine perspective.: Springer Science + Business Media, New York, NY; 2011 p.335-383. Available from: PsycINFO
650. Cavalcanti-Ribeiro P, Andrade-Nascimento M, Morais-De-Jesus M, De Medeiros GM, Daltro-Oliveira R, Conceição JO, et al. Post-traumatic stress disorder as a comorbidity: Impact on disease outcomes. Expert Review of Neurotherapeutics. 2012;12(8):1023-1037.
651. Choma TJ, Schuster JM, Norvell DC, Dettori JR, Chutkan NB. Fusion versus nonoperative management for chronic low back pain: do comorbid diseases or general health factors affect outcome? (Provisional abstract). Spine. 2011;36(21 Suppl):S87-95. doi: 10.1097/BRS.0b013e31822ef89e
652. Dikeos D, Georgantopoulos G. Medical comorbidity of sleep disorders. Curr Opin Psychiatry. 2011 Jul;24(4):346-54. doi: 10.1097/YCO.0b013e3283473375
653. Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: Dopamine as a putative mechanism. Sleep Medicine Reviews. 2013;17(3):173-183. Available from: PsycINFO. doi: 10.1016/j.smrv.2012.03.003
654. Hainsworth KR, Miller LA, Stolzman SC, Fidlin BM, Davies WH, Weisman SJ, et al. Pain as a Comorbidity of Pediatric Obesity. Infant, Child, and Adolescent Nutrition. 2012;4(5):315-320.
655. Inaba Y, Bergmann SR. Prognostic value of myocardial metabolic imaging with BMIPP in the spectrum of coronary artery disease: a systematic review. Journal of Nuclear Cardiology. 2010;17(1):61-70. doi: 10.1007/s12350-009-9157-y
656. Lake AE, Rains JC, Penzien DB, Lipchik GL. Headache and Psychiatric Comorbidity: Historical Context, Clinical Implications, and Research Relevance. Headache: The Journal of Head and Face Pain. 2005;45(5):493-506. Available from: PsycINFO. doi: 10.1111/j.1526-4610.2005.05101.x
657. Maizels M, Smitherman TA, Penzien DB. A Review of Screening Tools for Psychiatric Comorbidity in Headache Patients. Headache: The Journal of Head and Face Pain. 2006;46(Suppl 3):S98-S109. Available from: PsycINFO. doi: 10.1111/j.1526-4610.2006.00561.x
658. Marks JL, Colebatch AN, Buchbinder R, Edwards CJ. Pain management for rheumatoid arthritis and cardiovascular or renal comorbidity. Cochrane Database Syst Rev. 2011 (10):CD008952. doi: 10.1002/14651858.CD008952.pub2
659. Patel ARC, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. Expert Review of Respiratory Medicine. 2011;5(5):647-662.
660. Pompili M, Di Cosimo D, Innamorati M, Lester D, Tatarelli R, Martelletti P. Psychiatric comorbidity in patients with chronic daily headache and migraine: A selective overview including personality traits and suicide risk. The Journal of Headache and Pain. 2009;10(4):283-290. Available from: PsycINFO. doi: 10.1111/j.1468-2982.2003.00824.x
10.1007/s10194-009-0134-2
661. Radner H, Ramiro S, Buchbinder R, Landewe RB, van der Heijde D, Aletaha D. Pain management for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other spondylarthritis) and gastrointestinal or liver comorbidity. Cochrane Database Syst Rev. 2012;1:CD008951. doi: 10.1002/14651858.CD008951.pub2
662. Riddell MC, Burr J. Evidence-based risk assessment and recommendations for physical activity clearance: diabetes mellitus and related comorbidities11This paper is one of a selection of papers published in this Special Issue, entitled Evidence-based risk assessment and recommendations for physical activity clearance, and has undergone the Journal's usual peer review process. Applied Physiology, Nutrition, and Metabolism. 2011;36(1, Supplement 1):S154-S189.
663. Wu J, Zhu Q. Advances in studies on overlapping symptoms and comorbidity of irritable bowel syndrome. Chinese Journal of Gastroenterology. 2010;15(5):302-304.
664. de Rooij M, Steultjens MPM, Avezaat E, Häkkinen A, Klaver R, van der Leeden M, et al. Restrictions and contraindications for exercise therapy in patients with hip and knee osteoarthritis and comorbidity. Physical Therapy Reviews. 2013;18(2):101-111.
665. Stovner LJ, Hagen K. Hypertension-associated hypalgesia: a clue to the comorbidity of headache and other pain disorders. Acta neurologica Scandinavica. Supplementum. 2009 (189):46-50. doi: 10.1111/j.1600-0404.2009.01215.x

666. Blank R, Hobbs FDR, Zamorano J, Girerd X. A single-pill combination of amlodipine besylate and atorvastatin calcium (update). Drugs of Today. 2007;43(3):157-177. doi: 10.1358/dot.2007.43.3.1079878
667. Liu MG, Chen J. Preclinical research on pain comorbidity with affective disorders and cognitive deficits: Challenges and perspectives. Prog Neurobiol. 2014 May;116:13-32. doi: 10.1016/j.pneurobio.2014.01.003
668. Walker AK, Kavelaars A, Heijnen CJ, Dantzer R. Neuroinflammation and comorbidity of pain and depression. Pharmacol Rev. 2014;66(1):80-101. doi: 10.1124/pr.113.008144
669. Young G, Lareau C, Pierre B. One quintillion ways to have PTSD comorbidity: Recommendations for the disordered DSM-5. Psychological Injury and Law. 2014;7(1):61-74. Available from: PsycINFO. doi: 10.1007/s12207-014-9186-y
670. Li JX. Pain and depression comorbidity: A preclinical perspective. Behavioural Brain Research. 2015;276:92-98. Available from: Scopus. doi: 10.1016/j.bbr.2014.04.042
671. Arnow BA, Blasey CM, Lee J, Fireman B, Hunkeler EM, Dea R, et al. Relationships among depression, chronic pain, chronic disabling pain, and medical costs (Brief record). Psychiatric Services. 2009;60(3):344-350.
672. Kowal J, Overduin LY, Balfour L, Tasca GA, Corace K, Cameron DW. The role of psychological and behavioral variables in quality of life and the experience of bodily pain among persons living with HIV. Journal of pain and symptom management. 2008;36(3):247-58.
673. Kurtz ME, Kurtz JC, Given CW, Given BA. Patient optimism and mastery-do they play a role in cancer patients' management of pain and fatigue? Journal of pain and symptom management. 2008;36(1):1-10.
674. Morasco BJ, Dobscha SK. Prescription medication misuse and substance use disorder in VA primary care patients with chronic pain. General hospital psychiatry. 2008;30(2):93-9.
675. Zhu B, Zhao Z, Ye W, Marciniak MD, Swindle R. The cost of comorbid depression and pain for individuals diagnosed with generalized anxiety disorder (Brief record). Journal of Nervous and Mental Disease. 2009;197(2):136-139.
676. Small GW, Birkett M, Meyers BS, Koran LM, Bystritsky A, Nemeroff CB. Impact of physical illness on quality of life and antidepressant response in geriatric major depression. Fluoxetine Collaborative Study Group. Journal of the American Geriatrics Society. 1996;44(10):1220-5.
677. Gameroff MJ, Olfson M. Major depressive disorder, somatic pain, and health care costs in an urban primary care practice (Brief record). Journal of Clinical Psychiatry. 2006;67(8):1232-1239.
678. Scott KM, Browne MAO, McGee MA, Wells JE. Mental-physical comorbidity in Te Rau Hinengaro: The New Zealand Mental Health Survey. Australian and New Zealand Journal of Psychiatry. 2006 Oct;40(10):882-888. Available from: PsycINFO.
679. Tsao JC, Dobalian A, Stein JA. Illness burden mediates the relationship between pain and illicit drug use in persons living with HIV. Pain. 2005;119(1-3):124-32.
680. Bonin M, Norton GR, Frombach I, Asmundson GJ. PTSD in different treatment settings: a preliminary investigation of PTSD symptomatology in substance abuse and chronic pain patients. Depress Anxiety. 2000;11(3):131-3.
681. Grabe HJ, Meyer C, Hapke U, Rumpf HJ, Freyberger HJ, Dilling H, et al. Lifetime-comorbidity of obsessive-compulsive disorder and subclinical obsessive-compulsive disorder in northern Germany. European Archives of Psychiatry and Clinical Neuroscience. 2001;251(3):130-135. doi: 10.1007/s004060170047
682. Bonnewyn A, Katona C, Bruffaerts R, Haro JM, de Graaf R, Alonso J, et al. Pain and depression in older people: Comorbidity and patterns of help seeking. Journal of Affective Disorders. 2009;117(3):193-196. doi: 10.1016/j.jad.2009.01.012
683. Mao JJ, Armstrong K, Bowman MA, Xie SX, Kadakia R, Farrar JT. Symptom burden among cancer survivors: Impact of age and comorbidity. Journal of the American Board of Family Medicine. 2007;20(5):434-443. doi: 10.3122/jabfm.2007.05.060225
684. Mavandadi S, Sorkin DH, Rook KS, Newsom JT. Pain, positive and negative social exchanges, and depressive symptomatology in later life. Journal of Aging and Health. 2007;19(5):813-830. doi: 10.1177/0898264307305179
685. Scott K, McGee MA, Schaaf D, Baxter J. Mental-physical comorbidity in an ethnically diverse population. Social Science & Medicine. 2008 Mar;66(5):1165-1173. Available from: PsycINFO.
686. Sachs-Ericsson N, Kendall-Tackett K, Hernandez A. Childhood abuse, chronic pain, and depression in the National Comorbidity Survey. Child Abuse and Neglect. 2007;31(5):531-547. doi: 10.1016/j.chiabu.2006.12.007
687. Scott KM, Von Korff M, Alonso J, Angermeyer M, Bromet EJ, Bruffaert R, et al. Age patterns in the prevalence of DSM-IV depressive/anxiety disorders with and without physical co-morbidity. Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences. 2008 Nov;38(11):1659-1669. Available from: PsycINFO.
688. Westert GP, Satariano WA, Schellevis FG, Van Den Bos GAM. Patterns of comorbidity and the use of health services in the Dutch population. European Journal of Public Health. 2001;11(4):365-372. doi: 10.1093/eurpub/11.4.365
689. Von Strauss E, Fratiglioni L, Viitanen M, Forsell Y, Winblad B. Morbidity and comorbidity in relation to functional status: A community-based study of the oldest old (90+ years). Journal of the American Geriatrics Society. 2000;48(11):1462-1469.

690. van Nispen RM, de Boer MR, Hoeijmakers JG, Ringens PJ, van Rens GH. Co-morbidity and visual acuity are risk factors for health-related quality of life decline: five-month follow-up EQ-5D data of visually impaired older patients. Health Qual Life Outcomes. 2009;7:18. doi: 10.1186/1477-7525-7-18
691. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. Journal of Neurology, Neurosurgery and Psychiatry. 2010;81(4):428-432. doi: 0.1136/jnnp.2009.192492
692. Leiknes KA, Finset A, Moum T, Sandanger I. Current somatoform disorders in Norway: Prevalence, risk factors and comorbidity with anxiety, depression and musculoskeletal disorders. Social Psychiatry and Psychiatric Epidemiology. 2007;42(9):698-710. doi: 10.1007/s00127-007-0218-8
693. Radecki SE, Nissenson AR. Dialysis for chronic renal failure: Comorbidity and treatment differences by disease etiology. American Journal of Nephrology. 1989;9(2):115-123.
694. Shin DW, Nam JH, Kwon YC, Park SY, Bae DS, Park CT, et al. Comorbidity in disease-free survivors of cervical cancer compared with the general female population. Oncology. 2008;74(3-4):207-215. doi: 10.1159/000151368
695. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. Comorbidity delays diagnosis and increases disability at diagnosis in MS. Neurology. 2009;72(2):117-124. doi: 10.1212/01.wnl.0000333252.78173.5f
696. Vandvik PO, Lydersen S, Farup PG. Prevalence, comorbidity and impact of irritable bowel syndrome in Norway. Scandinavian Journal of Gastroenterology. 2006;41(6):650-656. doi: 10.1080/00365520500442542
697. Bröker LE, Hurenkamp GJ, Ter Riet G, Schellevis FG, Grundmeijer HG, Van Weert HC. Upper gastrointestinal symptoms, psychosocial co-morbidity and health care seeking in general practice: Population based case control study. BMC Family Practice. 2009;10:63. doi: 10.1186/1471-2296-10-63
698. Brown J, Berenson K, Cohen P. Documented and self-reported child abuse and adult pain in a community sample. The Clinical journal of pain. 2005;21(5):374-7.
699. Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. Neurology. 2000;55(5):624-9.
700. Allen AM, Allen SS, Lunos S, Pomerleau CS. Severity of withdrawal symptomatology in follicular versus luteal quitters: The combined effects of menstrual phase and withdrawal on smoking cessation outcome. Addictive Behaviors. 2010;35(6):549-552. Available from: PsycINFO. doi: 10.1016/j.addbeh.2010.01.003
701. Alschuler KN, Otis JD. Significant others' responses to pain in veterans with chronic pain and clinical levels of post-traumatic stress disorder symptomatology. Eur J Pain. 2013 Feb;17(2):245-54. doi: 10.1002/j.1532-2149.2012.00180.x
702. Andersson D, Magnusson H, Carstensen J, Borgquist L. Co-morbidity and health care utilisation five years prior to diagnosis for depression. A register-based study in a Swedish population. BMC Public Health. 2011;11:552. doi: 10.1186/1471-2458-11-552
703. Bell LM, Curran JA, Byrne S, Roby H, Suriano K, Jones TW, et al. High incidence of obesity co‐morbidities in young children: A cross‐sectional study. Journal of Paediatrics and Child Health. 2011;47(12):911-917. Available from: PsycINFO. doi: 10.1111/j.1440-1754.2011.02102.x
704. Chong SA, Abdin E, Nan L, Vaingankar JA, Subramaniam M. Prevalence and impact of mental and physical comorbidity in the adult Singapore population. Annals of the Academy of Medicine Singapore. 2012;41(3):105-114. doi: 10.1002/mpr.1351. [Epub ahead of print];
705. Coronado RA, Alappattu MJ, Hart DL, George SZ. Total Number and Severity of Comorbidities Do Not Differ Based on Anatomical Region of Musculoskeletal Pain. Journal of Orthopaedic and Sports Physical Therapy. 2011;41(7):477-485.
706. Dorsten BV, Weisberg JN. Psychological co-morbidities in patients with pain. In: Psychological co-morbidities of physical illness: A behavioral medicine perspective.: Springer Science + Business Media, New York, NY; 2011 p.275-310. Available from: PsycINFO
707. Gonzalez A, Boyle MH, Kyu HH, Georgiades K, Duncan L, MacMillan HL. Childhood and family influences on depression, chronic physical conditions, and their comorbidity: Findings from the ontario child health study. Journal of Psychiatric Research. 2012;46(11):1475-1482. Available from: PsycINFO. doi: 10.1016/j.jpsychires.2012.08.004
708. Lee MH, So ES. Impact of hypertension-related comorbidity on health-related quality of life: A population-based survey in South Korea. Asia-Pacific Journal of Public Health. 2012;24(5):753-763. Available from: PsycINFO. doi: 10.1177/1010539511431822
709. Marzolini S, Oh PI, Alter D, Stewart DE, Grace SL. Musculoskeletal Comorbidities in Cardiac Patients: Prevalence, Predictors, and Health Services Utilization. Archives of Physical Medicine and Rehabilitation. 2012;93(5):856-862.
710. Morone NE, Weiner DK, Herbeck Belnap B, Karp JF, Mazumdar S, Houck PR, et al. The impact of pain and depression on recovery after coronary artery bypass grafting. Psychosomatic Medicine. 2010;72(7):620-5. doi: 10.1097/PSY.0b013e3181e6df90
711. Perruccio AV, Katz JN, Losina E. Health burden in chronic disease: multimorbidity is associated with

self-rated health more than medical comorbidity alone. J Clin Epidemiol. 2012 Jan;65(1):100-6. doi: 10.1016/j.jclinepi.2011.04.013
712. Rannestad T, Skjeldestad FE. Co-morbidity and pain sites in long-term gynecological cancer survivors and women in the general population. Gynecol Oncol. 2012 Oct;127(1):168-71. doi: 10.1016/j.ygyno.2012.06.016
713. Subramaniam M, Abdin E, Vaingankar JA, Chong SA. Prevalence, correlates, comorbidity and severity of bipolar disorder: Results from the Singapore Mental Health Study. Journal of Affective Disorders. 2013;146(2):189-196. Available from: PsycINFO. doi: 10.1016/j.jad.2012.09.002
714. Wong WS, Fielding R. The co-morbidity of chronic pain, insomnia, and fatigue in the general adult population of Hong Kong: Prevalence and associated factors. Journal of Psychosomatic Research. 2012;73(1):28-34. Available from: PsycINFO. doi: 10.1016/j.jpsychores.2012.04.011
715. Thomas AM. An exploratory correlational study of chronic pain acceptance and trauma symptomatology in persons involved in Internet-based chronic pain support groups [Doctorate's thesis]: Spalding University; 2009. Available from: http://search.proquest.com/docview/1001920225?accountid=13552 http://primoapac01.hosted.exlibrisgroup.com/openurl/RMITU/RMIT_SERVICES_PAGE??url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:dissertation&genre=dissertations+%26+theses&sid=ProQ:PsycINFO&atitle=&title=An+exploratory+correlational+study+of+chronic+pain+acceptance+and+trauma+symptomatology+in+persons+involved+in+Internet-based+chronic+pain+support+groups.&issn=&date=2012-01-01&volume=&issue=&spage=&au=Thomas%2C+Ann+Marie&isbn=9781124696140&jtitle=&btitle=&rft_id=info:eric/
716. Strine TW, Kobau R, Chapman DP, Thurman DJ, Price P, Balluz LS. Psychological Distress, Comorbidities, and Health Behaviors among U.S. Adults with Seizures: Results from the 2002 National Health Interview Survey. Epilepsia. 2005;46(7):1133-1139.
717. Broderick JE, Vikingstad G. Frequent assessment of negative symptoms does not induce depressed mood. Journal of clinical psychology in medical settings. 2008;15(4):296-300.
718. Rastelli A, Taylor M, Villareal R, Jamalabadi-Majidi S, Gao F, Ellis M. A Double-Blind, Randomized, Placebo-Controlled Trial of High Dose Vitamin D Therapy on Musculoskeletal Pain and Bone Mineral Density in Anastrozole-Treated Breast Cancer Patients with Marginal Vitamin D Status. Cancer Research. 2010;64(24 Supplement):803. doi: 10.1158/0008-5472.SABCS-09-803
719. Landrø NI, Fors EA, Våpenstad LL, Holthe Ø, Stiles TC, Borchgrevink PC. The extent of neurocognitive dysfunction in a multidisciplinary pain centre population. Is there a relation between reported and tested neuropsychological functioning? Pain. 2013;154(7):972-7. doi: 10.1016/j.pain.2013.01.013
720. Mellbye A, Karlstad Ø, Skurtveit S, Borchgrevink PC, Fredheim OMS. Co‐morbidity in persistent opioid users with chronic non‐malignant pain in Norway. European Journal of Pain. 2014;18(8):1083-1093. Available from: PsycINFO. doi: 10.1002/j.1532-2149.2014.00449.x
721. Pugh MJ, Finley EP, Copeland LA, Wang CP, Noel PH, Amuan ME, et al. Complex comorbidity clusters in OEF/OIF veterans: the polytrauma clinical triad and beyond. Med Care. 2014 Feb;52(2):172-81. doi: 10.1097/mlr.0000000000000059
722. Alschuler KN, Otis JD. An examination of the impact of clinically significant levels of posttraumatic stress disorder symptomatology on the classification of pain as mild, moderate, or severe in a sample of veterans with chronic pain. Psychol Serv. 2014 Aug;11(3):273-80. doi: 10.1037/a0036201
723. Chelminski PR, Ives TJ, Felix KM, Prakken SD, Miller TM, Perhac JS, et al. A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. BMC Health Services Research. 2005;5:3. doi: 10.1186/1472-6963-5-3
724. de Tommaso M, Sardaro M, Serpino C, Costantini F, Vecchio E, Prudenzano MP, et al. Fibromyalgia comorbidity in primary headaches. Cephalalgia. 2009 Apr;29(4):453-64. doi: 10.1111/j.1468-2982.2008.01754.x
725. Heo M, Pietrobelli A, Wang D, Heymsfield SB, Faith MS. Obesity and Functional Impairment: Influence of Comorbidity, Joint Pain, and Mental Health. Obesity. 2009. doi: 10.1038/oby.2009.400
726. Sareen J, Cox BJ, Stein MB, Afifi TO, Fleet C, Asmundson GJG. Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. Psychosomatic Medicine. 2007;69(3):242-248. doi: 10.1097/PSY.0b013e31803146d8
727. Stych B, Dobrovolny D. Familial cold auto-inflammatory syndrome (FCAS): Characterization of symptomatology and impact on patients' lives. Current Medical Research and Opinion. 2008;24(6):1577-1582. doi: 10.1185/03007990802081543
728. Wiendels NJ, Van Haestregt A, Neven AK, Spinhoven P, Zitman FG, Assendelft WJJ, et al. Chronic frequent headache in the general population: Comorbidity and quality of life. Cephalalgia. 2006;26(12):1443-1450. doi: 10.1111/j.1468-2982.2006.01211.x
729. Caughey GE, Roughead EE, Vitry AI, McDermott RA, Shakib S, Gilbert AL. Comorbidity in the elderly with diabetes: Identification of areas of potential treatment conflicts. Diabetes Research and Clinical Practice. 2010;87(3):385-393. doi: 10.1016/j.diabres.2009.10.019
730. Frayne SM, Seaver MR, Loveland S, Christiansen CL, Spiro A, Parker VA, et al. Burden of medical illness in women with depression and posttraumatic stress disorder. Archives of internal medicine.

2004;164(12):1306-12.
731. Gill KM, Mishel M, Belyea M, Germino B, Germino LS, Porter L, et al. Triggers of uncertainty about recurrence and long-term treatment side effects in older African American and Caucasian breast cancer survivors. Oncology nursing forum. 2004;31(3):633-9.
732. Gureje O, Kola L, Ademola A, Olley BO. Profile, comorbidity and impact of insomnia in the Ibadan study of ageing. International Journal of Geriatric Psychiatry. 2009;24(7):686-693. doi: 10.1002/gps.2180
733. Sledjeski E, Speisman B, Dierker L. Does number of lifetime traumas explain the relationship between PTSD and chronic medical conditions? Answers from the National Comorbidity Survey-Replication (NCS-R). Journal of Behavioral Medicine. 2008 08;31(4):341-349.
734. Vaccarino AL, Sills TL, Evans KR, Kalali AH. Prevalence and association of somatic symptoms in patients with Major Depressive Disorder. Journal of affective disorders. 2008;110(3):270-6.
735. Sach TH, Barton GR, Doherty M, Muir KR, Jenkinson C, Avery AJ. The relationship between body mass index and health-related quality of life: comparing the EQ-5D, EuroQol VAS and SF-6D (Brief record). International Journal of Obesity. 2007;31(1):189-196.
736. Anttila P, Metsahonkala L, Mikkelsson M, Helenius H, Sillanpaa M. Comorbidity of other pains in schoolchildren with migraine or nonmigrainous headache. J Pediatr. 2001 Feb;138(2):176-80. doi: 10.1067/mpd.2001.112159
737. Coughlin JW, Edwards R, Buenaver L, Redgrave G, Guarda AS, Haythornthwaite J. Pain, catastrophizing, and depressive symptomatology in eating disorders. Clinical Journal of Pain. 2008;24(5):406-414. doi: 10.1097/AJP.0b013e3181633fc5
738. Ikaheimo P, Hartikainen S, Tuuponen T, Kiuttu J, Klaukka T. Comorbidity and medication load in adult asthmatics. Scand J Prim Health Care. 2005 Jun;23(2):88-94. doi: 10.1080/02813430510018473
739. Obermeyer CM, Schulein M, Hajji N, Azelmat M. Menopause in Morocco: symptomatology and medical management. Maturitas. 2002 Feb 26;41(2):87-95.
740. Sansone RA, Pole M, Dakroub H, Butler M. Childhood trauma, borderline personality symptomatology, and psychophysiological and pain disorders in adulthood. Psychosomatics. 2006 Mar-Apr;47(2):158-62. doi: 10.1176/appi.psy.47.2.158
741. Wijnhoven HA, Kriegsman DM, Hesselink AE, de Haan M, Schellevis FG. The influence of co-morbidity on health-related quality of life in asthma and COPD patients. Respir Med. 2003 May;97(5):468-75.
742. Saunders K, Merikangas K, Low NC, Von Korff M, Kessler RC. Impact of comorbidity on headache-related disability. Neurology. 2008 Feb 12;70(7):538-47. doi: 10.1212/01.wnl.0000297192.84581.21
743. Ahroni JH, Montgomery KF, Watkins BM. Laparoscopic adjustable gastric banding: Weight loss, co-morbidities, medication usage and quality of life at one year. Obesity Surgery. 2005;15(5):641-647. doi: 10.1381/0960892053923716
744. Lyketsos CG, Toone L, Tschanz J, Rabins PV, Steinberg M, Onyike CU, et al. Population-based study of medical comorbidity in early dementia and "Cognitive Impairment, No Dementia (CIND)". Association with functional and cognitive impairment: The Cache County Study. American Journal of Geriatric Psychiatry. 2005;13(8):656-664. doi: 10.1176/appi.ajgp.13.8.656
745. McDevitt DG. Symptomatology of chronic brucellosis. British Journal of Industrial Medicine. 1973;30(4):385-389.
746. Morse MS, Berg JS, TenWolde RL. Diffuse electrical injury: A study of 89 subjects reporting long-term symptomatology that is remote to the theoretical current pathway. IEEE Transactions on Biomedical Engineering. 2004;51(8):1449-1459. doi: 10.1109/tbme.2004.827343
747. Batki SL, Meszaros ZS, Strutynski K, Dimmock JA, Leontieva L, Ploutz-Snyder R, et al. Medical comorbidity in patients with schizophrenia and alcohol dependence. Schizophrenia Research. 2009;107(2-3):139-146. doi: 10.1016/j.schres.2008.10.016
748. Albert A, Altabre C, Baro F, Buendia E, Cabero A, Cancelo MJ, et al. Efficacy and safety of a phytoestrogen preparation derived from Glycine max (L.) Merr in climacteric symptomatology: a multicentric, open, prospective and non-randomized trial. Phytomedicine. 2002 Mar;9(2):85-92.
749. Ani C, Bazargan M, Hindman D, Bell D, Farooq MA, Akhanjee L, et al. Depression symptomatology and diagnosis: Discordance between patients and physicians in primary care settings. BMC Family Practice. 2008;9:1. doi: 10.1186/1471-2296-9-1
750. Fabri GM, Siqueira SR, Simione C, Nasri C, Teixeira MJ, Siqueira JT. Refractory craniofacial pain: is there a role of periodontal disease as a comorbidity? Arq Neuropsiquiatr. 2009 Jun;67(2B):474-9.
751. Newman AB, Naydeck BL, Sutton-Tyrrell K, Polak JF, Kuller LH. The role of comorbidity in the assessment of intermittent claudication in older adults. Journal of Clinical Epidemiology. 2001;54(3):294-300. doi: 10.1016/s0895-4356(00)00308-5
752. Wise TN, Wiltse CG, Iosifescu DV, Sheridan M, Xu JY, Raskin J. The safety and tolerability of duloxetine in depressed elderly patients with and without medical comorbidity. International journal of clinical practice. 2007;61(8):1283-93.
753. Andreadou E, Anagnostouli M, Vasdekis V, Kararizou E, Rentzos M, Kontaxis T, et al. The impact of comorbidity and other clinical and sociodemographic factors on health-related quality of life in Greek patients

with Parkinson's disease. Aging Ment Health. 2011 Sep;15(7):913-21. doi: 10.1080/13607863.2011.569477
754. Du Y, Heidemann C, Göwald A, Schmich P, Scheidt-Nave C. Prevalence and comorbidity of diabetes mellitus among non-institutionalized older adults in Germany - Results of the national telephone health interview survey German Health Update (GEDA) 2009. BMC Public Health. 2013;13:166. doi: 10.1186/1471-2458-13-166
755. Hollisaaz MT, Aghanassir M, Lorgard-Dezfuli-Nezad M, Assari S, Hafezie R, Ebrahiminia M. Medical Comorbidities After Renal Transplantation. Transplantation Proceedings. 2007;39(4):1048-1050.
756. Luijks H, Schermer T, Bor H, van Weel C, Lagro-Janssen T, Biermans M, et al. Prevalence and incidence density rates of chronic comorbidity in type 2 diabetes patients: an exploratory cohort study. BMC Med. 2012;10:128. doi: 10.1186/1741-7015-10-128
757. Marrie RA, Horwitz RI, Cutter G, Tyry T, Vollmer T. Association between comorbidity and clinical characteristics of MS. Acta Neurologica Scandinavica. 2011;124(2):135-141. Available from: PsycINFO. doi: 10.1111/j.1600-0404.2010.01436.x
758. Mignogna MD, Pollio A, Fortuna G, Leuci S, Ruoppo E, Adamo D, et al. Unexplained Somatic Comorbidities in Patients with Burning Mouth Syndrome: A Controlled Clinical Study. Journal of Orofacial Pain [Article]. 2011;25(2):131-140.
759. Nguyen RH, Veasley C, Smolenski D. Latent class analysis of comorbidity patterns among women with generalized and localized vulvodynia: preliminary findings. J Pain Res. 2013;6:303-9. doi: 10.2147/jpr.s42940
760. Ottman R, Lipton RB, Ettinger AB, Cramer JA, Reed ML, Morrison A, et al. Comorbidities of epilepsy: Results from the Epilepsy Comorbidities and Health (EPIC) survey. Epilepsia. 2011;52(2):308-315.
761. Schenk JM, Calip GS, Tangen CM, Goodman P, Parsons JK, Thompson IM, et al. Indications for and use of nonsteroidal antiinflammatory drugs and the risk of incident, symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. American journal of epidemiology [Randomized Controlled Trial; Research Support, N.I.H., Extramural]. 2012;176(2):156-63. doi: 10.1093/aje/kwr524
762. Suskind A, Berry S, Suttorp M, Elliott M, Hays R, Ewing B, et al. Health-related quality of life in patients with interstitial cystitis/bladder pain syndrome and frequently associated comorbidities. Quality of Life Research. 2013 (Preprints):1-5.
763. Strine TW, Chapman DP, Balluz LS. Population-Based U.S. Study of Severe Headaches in Adults: Psychological Distress and Comorbidities. Headache: The Journal of Head & Face Pain. 2006;46(2):223-232. Available from: s3h.
764. de Tommaso M, Federici A, Serpino C, Vecchio E, Franco G, Sardaro M, et al. Clinical features of headache patients with fibromyalgia comorbidity. The Journal of Headache and Pain. 2011;12(6):629-638. Available from: PsycINFO. doi: 10.1007/s11916-011-0207-1
10.1007/s10194-011-0377-6
765. Schneider S, Mohnen SM, Schiltenwolf M, Rau C. Comorbidity of low back pain: Representative outcomes of a national health study in the Federal Republic of Germany. European Journal of Pain. 2007;11(4):387-397. doi: 10.1016/j.ejpain.2006.05.005
766. Berti L, Bonfioli E, Castellazzi M, Fiorini I, Mazzi M, Muraro F, et al. Physico-physical comorbidity, poor health behaviour and health promotion in South Verona patients with functional psychoses. Psychiatrische Praxis. 2011. doi: 10.1055/s-0031-1277806
767. Comorbidity in adults with epilepsy--United States, 2010. MMWR Morb Mortal Wkly Rep. 2013 Nov 1;62(43):849-53.
768. Zhang N, Maffei A, Cerabona T, Pahuja A, Omana J, Kaul A. Reduction in obesity-related comorbidities: Is gastric bypass better than sleeve gastrectomy? Surgical Endoscopy and Other Interventional Techniques. 2013;27(4):1273-80. doi: 10.1007/s00464-012-2595-7
769. Kim SS, Oh KM, Richards K. Sleep disturbance, nocturnal agitation behaviors, and medical comorbidity in older adults with dementia: relationship to reported caregiver burden. Res Gerontol Nurs. 2014 Sep-Oct;7(5):206-14. doi: 10.3928/19404921-20140512-01
770. Britvić D, Antičević V, Kaliterna M, Lušić L, Beg A, Brajević-Gizdić I, et al. Comorbidities with Posttraumatic Stress Disorder (PTSD) among combat veterans: 15 years postwar analysis. International Journal of Clinical and Health Psychology. 2015;15(2):81-92. doi: 10.1016/j.ijchp.2014.11.002
771. Carroll LJ, Cassidy JD, Cote P. Frequency, timing, and course of depressive symptomatology after whiplash. Spine (Phila Pa 1976). 2006 Jul 15;31(16):E551-6. doi: 10.1097/01.brs.0000225979.26966.9e
772. Howland J, Bell NS, Hollander IE. Causes, types and severity of injury among army soldiers hospitalized with alcohol comorbidity. Addiction. 2007 Sep;102(9):1411-20. doi: 10.1111/j.1360-0443.2007.01908.x
773. Hestbaek L, Leboeuf-Yde C, Kyvik KO, Vach W, Russell MB, Skadhauge L, et al. Comorbidity with low back pain: a cross-sectional population-based survey of 12- to 22-year-olds... including commentary by Abdu WA. Spine. 2004 07;29(13):1483-1492.
774. McIntosh G, Hall H, Boyle C. Contribution of nonspinal comorbidity to low back pain outcomes. The Clinical journal of pain. 2006;22(9):765-9.
775. Franche RL, Carnide N, Hogg-Johnson S, Cote P, Breslin FC, Bultmann U, et al. Course, diagnosis, and treatment of depressive symptomatology in workers following a workplace injury: a prospective cohort study.

Can J Psychiatry. 2009 Aug;54(8):534-46.
776. Carroll LJ, Cassidy JD, Côté P. The Saskatchewan health and back pain survey: The prevalence and factors associated with depressive symptomatology in Saskatchewan adults. Canadian Journal of Public Health. 2000;91(6):459-464.
777. Holmberg S, Thelin A, Stiernström EL, Svärdsudd K. Low back pain comorbidity among male farmers and rural referents: A population-based study. Annals of Agricultural and Environmental Medicine. 2005;12(2):261-268.
778. Kroenke K, Price RK. Symptoms in the community: Prevalence, classification, and psychiatric comorbidity. Archives of Internal Medicine. 1993;153(21):2474-2480. doi: 10.1001/archinte.153.21.2474
779. Hestbaek L, Leboeuf-Yde C, Kyvik KO. Is comorbidity in adolescence a predictor for adult low back pain? A prospective study of a young population. BMC Musculoskeletal Disorders. 2006;7:29. doi: 10.1186/1471-2474-7-29
780. Olsson C, Petersson CJ. Clinical importance of comorbidity in patients with a proximal humerus fracture. Clinical Orthopaedics and Related Research. 2006 (442):93-99. doi: 10.1097/01.blo.0000194673.56764.0e
781. Seferlis T, Németh G, Carlsson AM, Gillström P. Acute low-back-pain patients exhibit a fourfold increase in sick leave for other disorders: a case-control study. Journal of spinal disorders. 1999;12(4):280-6.
782. Fichtel Å, Larsson B. Psychosocial impact of headache and comorbidity with other pains among Swedish school adolescents. Headache. 2002;42(8):766-775. doi: 10.1046/j.1526-4610.2002.02178.x
783. Ali MR, Rasmussen JJ, Monash JB, Fuller WD. Depression is associated with increased severity of co-morbidities in bariatric surgical candidates. Surgery for Obesity and Related Diseases. 2009;5(5):559-564. doi: 10.1016/j.soard.2008.10.015
784. Begre S, Traber M, Gerber M, von Kanel R. Change in pain severity with open label venlafaxine use in patients with a depressive symptomatology: an observational study in primary care. Eur Psychiatry. 2008 Apr;23(3):178-86. doi: 10.1016/j.eurpsy.2008.01.001
785. Laurell K, Larsson B, Eeg Olofsson O. Headache in schoolchildren: association with other pain, family history and psychosocial factors. Pain. 2005;119(1-3):150-8.
786. Hitt HC, McMillen RC, Thornton-Neaves T, Koch K, Cosby AG. Comorbidity of Obesity and Pain in a General Population: Results from the Southern Pain Prevalence Study. Journal of Pain. 2007;8(5):430-436. doi: 10.1016/j.jpain.2006.12.003
787. Breek JC, Hamming JF, De Vries J, van Berge Henegouwen DP, van Heck GL. The impact of walking impairment, cardiovascular risk factors, and comorbidity on quality of life in patients with intermittent claudication. J Vasc Surg. 2002 Jul;36(1):94-9.
788. Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. The American journal of psychiatry. 2007;164(6):900-9.
789. Shrestha NM, Sharma B, Van Ommeren M, Regmi S, Makaju R, Komproe I, et al. Impact of torture on refugees displaced within the developing world: Symptomatology among Bhutanese refugees in Nepal. Journal of the American Medical Association. 1998;280(5):443-448. doi: 10.1001/jama.280.5.443
790. Louie KS, St Laurent S, Forssen UM, Mundy LM, Pimenta JM. The high comorbidity burden of the hepatitis C virus infected population in the United States. BMC Infect Dis. 2012;12:86. doi: 10.1186/1471-2334-12-86
791. Maizels M, Burchette R. Somatic Symptoms in Headache Patients: The Influence of Headache Diagnosis, Frequency, and Comorbidity. Headache: The Journal of Head and Face Pain. 2004;44(10):983-993. Available from: PsycINFO. doi: 10.1111/j.1526-4610.2004.04192.x
792. Mongini F, Rota E, Deregibus A, Ferrero L, Migliaretti G, Cavallo F, et al. Accompanying symptoms and psychiatric comorbidity in migraine and tension-type headache patients. Journal of Psychosomatic Research. 2006;61(4):447-451. Available from: PsycINFO. doi: 10.1016/j.jpsychores.2006.03.005
793. Rajindrajith S, Devanarayana NM. Subtypes and Symptomatology of Irritable Bowel Syndrome in Children and Adolescents: A School-based Survey Using Rome III Criteria. J Neurogastroenterol Motil. 2012 Jul;18(3):298-304. doi: 10.5056/jnm.2012.18.3.298
794. Rajindrajith S, Devanarayana NM, Crispus Perera BJ. Rumination syndrome in children and adolescents: a school survey assessing prevalence and symptomatology. BMC Gastroenterol. 2012;12:163. doi: 10.1186/1471-230x-12-163
795. Bener A, Dafeeah EE, Chaturvedi SK, Bhugra D. Somatic symptoms in primary care and psychological comorbidities in Qatar: Neglected burden of disease. International Review of Psychiatry. 2013;25(1):100-106.
796. Devanarayana NM, Mettananda S, Liyanarachchi C, Nanayakkara N, Mendis N, Perera N, et al. Abdominal pain-predominant functional gastrointestinal diseases in children and adolescents: prevalence, symptomatology, and association with emotional stress. J Pediatr Gastroenterol Nutr. 2011 Dec;53(6):659-65. doi: 10.1097/MPG.0b013e3182296033
797. Wakeham K, Harding R, Bamukama-Namakoola D, Levin J, Kissa J, Parkes-Ratanshi R, et al. Symptom burden in HIV-infected adults at time of HIV diagnosis in rural Uganda. Journal of palliative medicine [Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2010;13(4):375-80. doi:

10.1089/jpm.2009.0259
798. Bahk WM, Park S, Jon DI, Yoon BH, Min KJ, Hong JP. Relationship between painful physical symptoms and severity of depressive symptomatology and suicidality. Psychiatry Res. 2011 Oct 30;189(3):357-61. doi: 10.1016/j.psychres.2011.01.009
799. Bargren AE, Repplinger D, Chen H, Sippel RS. Can biochemical abnormalities predict symptomatology in patients with primary hyperparathyroidism? J Am Coll Surg. 2011 Sep;213(3):410-4. doi: 10.1016/j.jamcollsurg.2011.06.401
800. Bener A, Ghuloum S, Abou-Saleh M. Prevalence, symptom patterns and comorbidity of anxiety and depressive disorders in primary care in Qatar. Social Psychiatry and Psychiatric Epidemiology. 2012;47(3):439-446.
801. Utriyaprasit K, Moore SM, Chaiseri P. Recovery after coronary artery bypass surgery: effect of an audiotape information programme. Journal of advanced nursing [Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2010;66(8):1747-59. doi: 10.1111/j.1365-2648.2010.05334.x
802. Aucott JN, Rebman AW, Crowder LA, Kortte KB. Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: Is there something here? Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care & Rehabilitation. 2013;22(1):75-84. Available from: PsycINFO. doi: 10.1007/s11136-012-0126-6
803. Hurwitz EL, Morgenstern H. The effects of comorbidity and other factors on medical versus chiropractic care for back problems... including commentary by Carey TS. Spine. 1997 10;22(19):2254-2264.
804. Chang WK, Wu HL, Yang CS, Chang KY, Liu CL, Chan KH, et al. Effect on pain relief and inflammatory response following addition of tenoxicam to intravenous patient-controlled morphine analgesia: a double-blind, randomized, controlled study in patients undergoing spine fusion surgery. Pain medicine (Malden, Mass.). 2013;14(5):736-48. doi: 10.1111/pme.12067
805. Gill M, Drendel AL, Weisman SJ. Parent satisfaction with acute pediatric pain treatment at home. Clinical journal of pain. 2013;29(1):64-9. doi: 10.1097/AJP.0b013e3182454a9e
806. Aillon J-L, Ndetei D, Khasakhala L, Ngari W, Achola H, Akinyi S, et al. Prevalence, types and comorbidity of mental disorders in a Kenyan primary health centre. Social Psychiatry and Psychiatric Epidemiology. 2014;49(8):1257-1268.
807. Brooke KJ, Faux SG, Wilson SF, Liauw W, Bowman M, Klein L. Outcomes of motor vehicle crashes with fracture: a pilot study of early rehabilitation interventions. Journal of rehabilitation medicine. 2014;46(4):335-40. doi: 10.2340/16501977-1275
808. Hermsen LA, Leone SS, Smalbrugge M, Dekker J, van der Horst HE. Frequency, severity and determinants of functional limitations in older adults with joint pain and comorbidity: results of a cross-sectional study. Arch Gerontol Geriatr. 2014 Jul-Aug;59(1):98-106. doi: 10.1016/j.archger.2014.02.006
809. Hermsen LA, Smalbrugge M, van der Wouden JC, Leone SS, Dekker J, van der Horst HE. Trajectories of physical functioning and their prognostic indicators: a prospective cohort study in older adults with joint pain and comorbidity. Maturitas. 2014 Aug;78(4):316-22. doi: 10.1016/j.maturitas.2014.05.020
810. King LA, Priest KC, Nutt J, Chen Y, Chen Z, Melnick M, et al. Comorbidity and functional mobility in persons with Parkinson disease. Arch Phys Med Rehabil. 2014 Nov;95(11):2152-7. doi: 10.1016/j.apmr.2014.07.396
811. Remoortel H, Hornikx M, Langer D, Burtin C, Everaerts S, Verhamme P, et al. Risk factors and comorbidities in the preclinical stages of chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2014;189(1):30-8. doi: 10.1164/rccm.201307-1240OC
812. Wilson K, Heyde R, Sparks M, Hammerschmidt K, Pleimann D, Ranz E, et al. The impact of demographic factors and comorbidities on distal radius fracture outcomes. Hand. 2014;9(1):80-86.
813. Haukka E, Leino Arjas P, Solovieva S, Ranta R, Viikari Juntura E, Riihimäki H. Co-occurrence of musculoskeletal pain among female kitchen workers. International archives of occupational and environmental health. 2006;80(2):141-8.
814. Koopmans RT, van Hell ME, de Jongh F, Froeling PG, van den Hoogen HJ, van Weel C. [The course of Alzheimer's disease in a group of nursing home patients: epidemiology, (co)morbidity and mortality]. Ned Tijdschr Geneeskd. 1991 May 11;135(19):845-50.
815. Huppe A, Raspe H. [Amplified back pain and comorbidity in the population]. Schmerz. 2009 Jun;23(3):275-8, 280-3. doi: 10.1007/s00482-009-0783-8
816. Molenaar EA, Numans ME, van Ameijden EJ, Grobbee DE. [Considerable comorbidity in overweight adults: results from the Utrecht Health Project]. Ned Tijdschr Geneeskd. 2008 Nov 8;152(45):2457-63.
817. Beutel ME, Hessel A, Schwarz R, Brähler E. Prevalence of urinary incontinence in the German population: Comorbidity, quality of life, determinants. Prävalenz der urininkontinenz in der deutschen bevölkerung: Komorbidität, lebensqualität, einflussgrößen. 2005;44(3):232-238. doi: 10.1007/s00120-005-0791-y
818. Carlsson GE, Svärdström G. A survey of the symptomatology of a series of 299 patients with stomatognathic dysfunction. Ett bettfysiologiskt patientmaterial. En översikt av symtombild hos och behandling av 299 patienter. 1971;64(12):889-899.

819. Cope R. Interet d'un produit natural, effidigest(TM) sur la symtomatologie des digestions difficiles avec constipation [The significance of the natural product Effidigest® on the symptomatology of difficult digestion with constipation]. Medecine et Chirurgie Digestives. 1997;26(7):327-329.
820. Guillem E, Pelissolo A, Lepine JP. Epidemiology and comorbidity of migraine and mental disorders. Troubles mentaux et migraine: Donnees epidemiologiques. 1999;25(5):436-442.
821. Härter M, Hahn D, Baumeister H, Reuter K, Wunsch A, Bengel J. Comorbidity in patients with musculoskeletal and cardiovascular diseases: Prevalence rates, diagnosis and consequences for rehabilitation. Komorbidität bei patienten mit muskuloskelettalen und kardiovaskulären erkrankungen: Prävalenzen, diagnosen and konsequenzen für die rehabilitation. 2004;12(3):162-167. doi: 10.1007/s10389-004-0032-7
822. Marquant T, Bruffaerts R, Bonnewyn A, Demyttenaere K. Mental and somatic comorbidity of hypertension in the Belgian general population. Mentale en somatische comorbiditeit van hypertensie in de Belgische bevolking. 2009;65(8):334-342. doi: 10.2143/tvg.65.08.2000519
823. Matyášová Z, Novotná B, Matulová M, Dolina J, Kroupa R, Láníková Z, et al. The relation of GERD, bronchial asthma and symptomatology from ear, nose and throught regions. Vztah refluxní choroby jícnu k astmatu bronchiale a horním cestám dýchacím. 2005;51(12):1341-1350.
824. Navas Collado E, Muñoz García JJ, García Moja LC. Fibromyalgia: A rheumatologic disease with high psychopatological comorbidity. Fibromialgia: Una enfermedad reumatológica con alta comorbilidad psicopatológica. 2003;19(6):253-264.
825. Schricker HH. Report on a few cases of 'Bornholm disease'. Infectiousness and symptomatology illustrated by family infections (German). Zeitschrift fur Allgemeinmedizin. 1975;51(6):282-285.
826. Stojanovic-Špehar S, Skočilić A, Blažekovic-Milaković S, Vuković H, Kumbrija S. Depression and comorbidity in family medicine registrars' surgeries - Pilot research. Depresija i komorbiditetne bolesti u ambulantama liječnika specijalizanata obiteljske medicine - Pilot istraživanje. 2007;37(1-2):5-14.
827. Van Boven B, Bruffaerts R, Bonnewyn A, Demyttenaere K. Somatic and mental comorbidity of chronic headache in the Belgian general population. Somatische en mentale comorbiditeit van chronische hoofdpijn in de Belgische algemene bevolking. 2009;65(9):398-406. doi: 10.2143/tvg.65.09.2000533
828. Yaluğ I, Özdemir S, Aker AT. Opioid dependency with posttraumatic stress disorder and cronic pain comorbidity. Travma sonrasi stres bozukluğu ve kronik ağri birlikteliği zemininde opioid bağimliliği. 2008;46(4):200-205.
829. Basler HD, Hesselbarth S, Kaluza G, Schuler M, Sohn W, Nikolaus T. [Comorbidity, multiple medication, and well-being in elderly patients with chronic pain]. Schmerz. 2003 Aug;17(4):252-60. doi: 10.1007/s00482-003-0231-0
830. Beutel ME, Weidner K, Brähler E. Chronic pelvic pain of women and its co-morbidity. Der chronische unterbauchschmerz der frau und seine komorbidität. 2005;65(1):61-67. doi: 10.1055/s-2004-830503
831. Bozzatello JR. [Relationship between craniofacial architecture and retained lower third molar. Its' symptomatology]. Rev Fac Cien Med Univ Nac Cordoba. 2006;63(2 Suppl):38-42.
832. Kratzsch KH, Furstenau M, Zimmermann S. [Ulcer anamnesis and gastroduodenoscopic findings--a contribution to the symptomatology of gastroduodenal ulcers]. Z Gesamte Inn Med. 1979 Sep 15;34(18):530-4.
833. Collado EN, Garcia JJM, Moja LCG. Fibromialgia: una enfermedad reumatológica con alta comorbilidad psicopatológica = Fibromyalgia: a rheumatologic disease with high psychopathological comorbidity. Anales de psiquiatria. 2003 Jun;19(6):253-264. Available from: PsycINFO.
834. Fiehn C, Kessler S. [Is the treatment response in elderly patients with rheumatoid arthritis diminished? Results of a prospective study over 3 months]. Zeitschrift für Rheumatologie. 2009;68(1):69-74.
835. Lemogne C, Smagghe PO, Djian MC, Caroli F. La douleur chronique en psychiatrie : comorbidité et hypothèses / Chronic pain and psychiatry: comorbidity and hypothesis. Annales médico-psychologiques. 2004 Jun;162(5):343-350. Available from: PsycINFO.
836. Pinto-Meza A, Serrano-Blanco A, Codony M, Reneses B, Von Korff M, Haro JM, et al. Prevalence and physical-mental comorbidity of chronic back and neck pain in Spain: Results from the ESEMeD Study. Prevalencia y comorbilidad física y mental del dolor dorsal y cervical crónicos en España: Resultados del estudio ESEMeD. 2006;127(9):325-330. doi: 10.1157/13092313
837. Radat F, Irachabal S, Swendsen J, Henry P. [Analgesic abuse and psychiatric comorbidity in headache patients]. Encephale. 2002 Sep-Oct;28(5 Pt 1):466-71.
838. Torres-Garate R, Alvarez-Rodriguez E, Bilbao Ormazabal N, Ciguenza R, Perez Perez J, Millana C, et al. [Abdominal pain, hypovolemic shock and comorbidity]. An Med Interna. 2004 Dec;21(12):615-6.
839. Westhoff G, Weber C, Zink A. [Comorbidity in rheumatoid arthritis of early onset. Effects on outcome parameters]. Z Rheumatol. 2006 Oct;65(6):487-8, 490-4, 496. doi: 10.1007/s00393-006-0102-z
840. Araújo, Correa de F, de Mattos A. Prevalence and comorbidity of pain and fatigue in women with breast cancer [Portuguese]. Revista da Escola de Enfermagem da USP. 2011;45(2):508-514. Available from: c8h. doi: S0080-62342011000200029
841. Baumeister H, Härter M. Psychological comorbidity in patients with musculoskeletal diseases. Psychische Komorbidität bei muskuloskelettalen Erkrankungen. 2011;54(1):52-58.
842. Lipczyński W, Dobrowolska-Glazar B, Dobrowolski ZF. [Comparison of self-estimation of disuric

disorders gauged IPSS scale and qualities of lives QoL with self-estimation of sexual life gauged by IIEF-5 scale]. Przeglad lekarski [Comparative Study; English Abstract; Randomized Controlled Trial]. 2012;69(6):247-52.
843. Mattioli S, Farioli A, Curti S, Lodi V, Zanardi F, Bonfiglioli R, et al. [COMMUNITY: project proposal for a multicenter study on musculoskeletal comorbidity among nursing staff]. G Ital Med Lav Ergon. 2010 Jul-Sep;32(3):227-30.
844. Mehnert A, Hund B, Härter M. Komorbidität psychischer störungen und psychischer belastung bei krebspatienten: Häufigkeiten und besonderheiten der diagnostik. Nervenheilkunde: Zeitschrift für interdisziplinaere Fortbildung. 2011;30(3):117-123. Available from: PsycINFO.
845. Morfeld M, Friedrichs A. [Psychological comorbidity. Diagnosis and indications for further treatment in medical rehabilitation]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2011 Jan;54(1):90-7. doi: 10.1007/s00103-010-1188-7
846. Pflugmacher R, Bornemann R, Koch EM, Hausmann D, Otten LA, Goost H, et al. [Comparative findings of balloon kyphoplasty in patients with vertebral fractures due to osteoporosis, metastases and myeloma]. Zeitschrift für Orthopädie und Unfallchirurgie [Clinical Trial; Controlled Clinical Trial; English Abstract;]. 2012;150(2):198-204. doi: 10.1055/s-0031-1280230
847. Reuter M, Jecht M, Bierwirth R, Ca?ens S, Brosz M, Prien M, et al. Diabetic Polyneuropathy and Related Comorbidities: Results of the GloDi Project. Diabetologie und Stoffwechsel. 2009;4(4):230-237.
848. Şahin S, Kaya B. Kronik ağri yakinmasi olan ve osteomiyelit belirtileriyle kendini gösteren bir yapay bozukluk olgusu. Klinik Psikiyatri Dergisi: The Journal of Clinical Psychiatry. 2009;12(3):147-152. Available from: PsycINFO.
849. Galvan P, Fernandez E, Fonseca J. Residual symptoms in elderly patients with depression. [Spanish]. Semergen. 2012;38(5):285-91. doi: 10.1016/j.semerg.2011.08.006
850. Bridou M, Aguerre C. [Premenstrual symptomatology, somatization and physical anhedonia]. Encephale. 2013 Dec;39(6):432-8. doi: 10.1016/j.encep.2012.08.003
851. Erlenwein J, Schlink J, Pfingsten M, Hinz J, Bauer M, Quintel M, et al. [Pre-existing pain as comorbidity in postoperative acute pain service]. Anaesthesist. 2013 Oct;62(10):808-16. doi: 10.1007/s00101-013-2224-4
852. Ruetten S, Komp M, Hahn P, Oezdemir S. [Decompression of lumbar lateral spinal stenosis: full-endoscopic, interlaminar technique]. Operative Orthopädie und Traumatologie. 2013;25(1):31-46. doi: 10.1007/s00064-012-0195-2
853. Blozik E, Dubben HH, Wagner HO, Scherer M. [Comorbidity in medical guidelines: comparison of the current state, epidemiologic models and expert opinion]. Z Evid Fortbild Qual Gesundhwes. 2014;108(4):219-28. doi: 10.1016/j.zefq.2014.02.001
854. Chernyshov OV. [A clinic and pathway comorbidity aetiology of the somatoform disorder, abuse syndromes and addictions at adolescent age]. Lik Sprava. 2014 Mar-Apr (3-4):44-51.
855. Pae CU, Masand PS, Marks DM, Krulewicz S, Peindl K, Mannelli P, et al. History of depressive and/or anxiety disorders as a predictor of treatment response: a post hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release in patients with fibromyalgia. Progress in neuro psychopharmacology & biological psychiatry. 2009;33(6):996-1002.
856. McCormick WC, Kukull WA, van Belle G, Bowen JD, Teri L, Larson EB. Symptom patterns and comorbidity in the early stages of Alzheimer's disease. J Am Geriatr Soc. 1994 May;42(5):517-21.
857. Evans-Lacko SE, Zeber JE, Gonzalez JM, Olvera RL. Medical comorbidity among youth diagnosed with bipolar disorder in the United States. Journal of Clinical Psychiatry. 2009;70(10):1461-1466. doi: 10.4088/JCP.08m04871
10.1097/JGP.0b013e318157c5b1
858. Seng JS, Graham-Bermann SA, Clark MK, McCarthy AM, Ronis DL. Posttraumatic stress disorder and physical comorbidity among female children and adolescents: Results from service-use data. Pediatrics. 2005;116(6):e767-76. doi: 10.1542/peds.2005-0608
859. Martin-Merino E, Ruigomez A, Johansson S, Wallander MA, Garcia-Rodriguez LA. Study of a cohort of patients newly diagnosed with depression in general practice: prevalence, incidence, comorbidity, and treatment patterns. Prim Care Companion J Clin Psychiatry. 2010;12(1):PCC 08m00764. doi: 10.4088/PCC.08m00764blu
860. Wallander MA, Johansson S, Ruigomez A, Garcia Rodriguez LA, Jones R. Dyspepsia in general practice: incidence, risk factors, comorbidity and mortality. Fam Pract. 2007 Oct;24(5):403-11. doi: 10.1093/fampra/cmm050
861. Kang JH, Chen YH, Lin HC. Comorbidity profiles among patients with ankylosing spondylitis: a nationwide population-based study. Ann Rheum Dis. 2010 Jun;69(6):1165-8. doi: 10.1136/ard.2009.116178
862. Abbiati C, Pricolo R, Montani A, Vimercati ME. Cervical rheumatoid arthritis. Description of a case with neurological symptomatology and survey of the literature. Minerva Medica. 1989;80(6):603-607.
863. Adrian M, Van Truong M, Osazuwa T. Measuring levels of comorbidity in drug user* emergency patients treated in Ontario hospitals. Substance Use and Misuse. 2007;42(2-3):199-224. doi: 10.1080/10826080601141909
864. Luber MP, Hollenberg JP, Williams-Russo P, Didomenico TN, Meyers BS, Alexopoulos GS, et al.

Diagnosis, treatment, comorbidity, and resource utilization of depressed patients in a general medical practice. International Journal of Psychiatry in Medicine. 2000;30(1):1-13.
865. Huitema HOM, Van Den Akker M, Buntinx F, Muris JW, Metsemakers JFM, Knottnerus JA. Comorbidity of chronic gastro-intestinal disorders. A cross-sectional analysis in a large general practice population in the Netherlands. Archives of Public Health. 2000;58(2):51-65.
866. Wu EQ, Birnbaum H, Mareva M, Parece A, Huang Z, Mallett D, et al. Interstitial cystitis: Cost, treatment and co-morbidities in an employed population. PharmacoEconomics. 2006;24(1):55-65. doi: 10.2165/00019053-200624010-00005
867. Walker EA, Katon WJ, Jemelka RP, Roy-Byrne PP. Comorbidity of gastrointestinal complaints, depression, and anxiety in the Epidemiologic Catchment Area (ECA) Study. American Journal of Medicine. 1992;92(1 A):26S-30S.
868. Cicero TJ, Wong G, Tian Y, Lynskey M, Todorov A, Isenberg K. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: data from an insurance claims database. Pain. 2009 Jul;144(1-2):20-7. doi: 10.1016/j.pain.2009.01.026
869. Hogel J, Rieker RJ, Eisele R, Schmid E. Influence of age, comorbidity, type of operation and other variables on lethality and duration of post-operative hospital stay in patients with peptic ulcer. An analysis of 303 surgically treated patients. Langenbecks Arch Chir. 1996;381(4):201-6.
870. Crémieux P-Y, Ledoux S, Clerici C, Cremieux F, Buessing M. The Impact of Bariatric Surgery on Comorbidities and Medication Use Among Obese Patients. Obesity Surgery. 2010;20(7):861-870.
871. Mark TL, Dilonardo J, Vandivort R, Miller K. Psychiatric and medical comorbidities, associated pain, and health care utilization of patients prescribed buprenorphine. Journal of Substance Abuse Treatment. 2013;44(5):481-487.
872. Nuno-Solinis R, Rodriguez-Pereira C, Alonso-Moran E, Orueta JF. Comorbidity and healthcare expenditure in women with osteoporosis living in the basque country (Spain). J Osteoporos. 2014;2014:205954. doi: 10.1155/2014/205954
873. Dupont JS, Jr., Brown CE. Comorbidity of pterygoid hamular area pain and TMD. Cranio. 2007 Jul;25(3):172-6.
874. Ritzwoller DP, Crounse L, Shetterly S, Rublee D. The association of comorbidities, utilization and costs for patients identified with low back pain (Brief record). BMC Musculoskeletal Disorders. 2006;7:72. doi: 10.1186/1471-2474-7-72
875. Schechtman KB, Kutner NG, Wallace RB, Buchner DM, Ory MG. Gender, self-reported depressive symptoms, and sleep disturbance among older community-dwelling persons. FICSIT group. Frailty and Injuries: Cooperative Studies of Intervention Techniques. Journal of psychosomatic research. 1997;43(5):513-27.
876. Holman AJ. Positional Cervical Spinal Cord Compression and Fibromyalgia: A Novel Comorbidity With Important Diagnostic and Treatment Implications. Journal of Pain. 2008;9(7):613-622. doi: 10.1016/j.jpain.2008.01.339
877. Kadam UT, Jordan K, Croft PR. Clinical comorbidity in patients with osteoarthritis: A case-control study of general practice consumers in England and Wales. Annals of the Rheumatic Diseases. 2004;63(4):408-414. doi: 10.1136/ard.2003.007526
878. Fleming ST, Pursley HG, Newman B, Pavlov D, Chen K. Comorbidity as a predictor of stage of illness for patients with breast cancer. Medical Care. 2005 02;43(2):132-140.
879. Ruigomez A, Rodriguez LA, Wallander MA, Johansson S, Jones R. Chest pain in general practice: incidence, comorbidity and mortality. Fam Pract. 2006 Apr;23(2):167-74. doi: 10.1093/fampra/cmi124
880. Caughey GE, Roughead EE, Shakib S, Vitry AI, Gilbert AL. Co-morbidity and potential treatment conflicts in elderly heart failure patients: A retrospective, cross-sectional study of administrative claims data. Drugs & Aging. 2011;28(7):575-581. Available from: PsycINFO. doi: 10.2165/11591090-000000000-00000
881. Chen Y-C, Tang C-H, Ng K, Wang S-J. Comorbidity profiles of chronic migraine sufferers in a national database in Taiwan. The Journal of Headache and Pain. 2012;13(4):311-319. Available from: PsycINFO. doi: 10.1007/s10194-012-0447-4
882. Ghate SR, Haroutiunian S, Winslow R, McAdam-Marx C. Cost and Comorbidities Associated with Opioid Abuse in Managed Care and Medicaid Patients in the United States: A Comparison of Two Recently Published Studies. Journal of Pain & Palliative Care Pharmacotherapy. 2010;24(3):251-258.
883. Gore M, Tai K-S, Chandran A, Zlateva G, Leslie D. Clinical comorbidities, treatment patterns, and healthcare costs among patients with fibromyalgia newly prescribed pregabalin or duloxetine in usual care. Journal of Medical Economics. 2012;15(1):19-31.
884. Gore M, Tai K-S, Sadosky A, Leslie D, Stacey BR. Clinical comorbidities, treatment patterns, and direct medical costs of patients with osteoarthritis in usual care: a retrospective claims database analysis. Journal of Medical Economics. 2012;14(4):497-507.
885. Toldo I, Perissinotto E, Menegazzo F, Boniver C, Sartori S, Salviati L, et al. Comorbidity between headache and epilepsy in a pediatric headache center. The journal of headache and pain. 2010;11(3):235-240.
886. Brook R, Kleinman N, Choung R, Smeeding J, Talley N. Excess Comorbidity Prevalence and Cost Associated with Functional Dyspepsia in an Employed Population. Digestive Diseases and Sciences.

2012;57(1):109-118.
887. Peter W, Dekker J, Tilbury C, Tordoir R, Verdegaal S, Onstenk R, et al. The association between comorbidities and pain, physical function and quality of life following hip and knee arthroplasty. Rheumatology International. 2015;35(7):1233-41. doi: 10.1007/s00296-015-3211-7
888. Chohan S, Becker MA, MacDonald PA, Chefo S, Jackson RL. Women with gout: efficacy and safety of urate-lowering with febuxostat and allopurinol. Arthritis care & research. 2012;64(2):256-61. doi: 10.1002/acr.20680
889. Kroenke K, Theobald D, Norton K, Sanders R, Schlundt S, McCalley S, et al. The Indiana Cancer Pain and Depression (INCPAD) trial Design of a telecare management intervention for cancer-related symptoms and baseline characteristics of study participants. General hospital psychiatry. 2009;31(3):240-53.
890. Leong IY, Farrell MJ, Helme RD, Gibson SJ. The relationship between medical comorbidity and self-rated pain, mood disturbance, and function in older people with chronic pain. J Gerontol A Biol Sci Med Sci. 2007 May;62(5):550-5.
891. van den Beuken-van Everdingen MHJ, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Quality of Life and Non-Pain Symptoms in Patients with Cancer. Journal of Pain and Symptom Management. 2009;38(2):216-233. doi: 10.1016/j.jpainsymman.2008.08.014
892. Venturino A, Comandini D, Granetto C, Audisio RA, Castiglione F, Rosso R, et al. Formestane is feasible and effective in elderly breast cancer patients with comorbidity and disability. Breast Cancer Research and Treatment. 2000;62(3):217-222. doi: 10.1023/a:1006490524736
893. Sebastian P, Varghese C, Sankaranarayanan R, Zaina CP, Nirmala G, Jeevy G, et al. Evaluation of symptomatology in planning palliative care. Palliative Medicine. 1993;7(1):27-34.
894. Rana A, Chisholm GD, Rashwan HM, Salim A, Merrick MV, Elton RA. Symptomatology of metastatic prostate cancer: prognostic significance. Br J Urol. 1994 Jun;73(6):683-6.
895. Vickers MM, Powell ED, Asmis TR, Jonker DJ, Hilton JF, O'Callaghan CJ, et al. Comorbidity, age and overall survival in patients with advanced pancreatic cancer - results from NCIC CTG PA.3: a phase III trial of gemcitabine plus erlotinib or placebo. Eur J Cancer. 2012 Jul;48(10):1434-42. doi: 10.1016/j.ejca.2011.10.035
896. Guenette JP, Lopez MJ, Kim E, Dupuy DE. Solitary painful osseous metastases: correlation of imaging features with pain palliation after radiofrequency ablation--a multicenter american college of radiology imaging network study. Radiology. 2013;268(3):907-15. doi: 10.1148/radiol.13122398
897. Naumann P, Habermehl D, Welzel T, Debus J, Combs SE. Outcome after neoadjuvant chemoradiation and correlation with nutritional status in patients with locally advanced pancreatic cancer. Strahlentherapie und Onkologie : Organ der Deutschen Röntgengesellschaft ... [et al]. 2013;189(9):745-52. doi: 10.1007/s00066-013-0393-3
898. Nguyen LM, Rhondali W, Cruz M, Hui D, Palmer L, Kang DH, et al. Frequency and predictors of patient deviation from prescribed opioids and barriers to opioid pain management in patients with advanced cancer. Journal of pain and symptom management. 2013;45(3):506-16. doi: 10.1016/j.jpainsymman.2012.02.023
899. Ohno T, Thinh DH, Kato S, Devi CR, Tung NT, Thephamongkhol K, et al. Radiotherapy concurrently with weekly cisplatin, followed by adjuvant chemotherapy, for N2-3 nasopharyngeal cancer: a multicenter trial of the Forum for Nuclear Cooperation in Asia. Journal of radiation research. 2013;54(3):467-73. doi: 10.1093/jrr/rrs115
900. Vissers PAJ, Thong MSY, Pouwer F, Zanders MMJ, Coebergh JWW, van de Poll-Franse LV. The impact of comorbidity on Health-Related Quality of Life among cancer survivors: Analyses of data from the PROFILES registry. Journal of Cancer Survivorship. 2013;7(4):602-613. Available from: PsycINFO. doi: 10.1007/s11764-013-0299-1
901. Bernhard J, Dietrich D, Glimelius B, Bodoky G, Scheithauer W, Herrmann R. Clinical benefit response in pancreatic cancer trials revisited. Oncology research and treatment. 2014;37(1-2):42-8. doi: 10.1159/000357965
902. Windyga J, Lin VW, Epstein JD, Ito D, Xiong Y, Abbuehl BE, et al. Improvement in health-related quality of life with recombinant factor IX prophylaxis in severe or moderately severe haemophilia B patients: Results from the BAX326 Pivotal Study. Haemophilia. 2014;20(3):362-8. doi: 10.1111/hae.12315
903. Wodajo FM. CORR Insights: What is the effect of advanced age and comorbidity on postoperative morbidity and mortality after musculoskeletal tumor surgery? Clin Orthop Relat Res. 2014 Dec;472(12):3979-81. doi: 10.1007/s11999-014-3951-9
904. Kroenke K, Bair MJ, Damush TM, Wu J, Hoke S, Sutherland J, et al. Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. JAMA : the journal of the American Medical Association. 2009;301(20):2099-110.
905. Penninx BW, Rejeski WJ, Pandya J, Miller ME, Di Bari M, Applegate WB, et al. Exercise and depressive symptoms: a comparison of aerobic and resistance exercise effects on emotional and physical function in older persons with high and low depressive symptomatology. J Gerontol B Psychol Sci Soc Sci. 2002 Mar;57(2):P124-32.
906. Arnold LM, Hudson JI, Keck Jr PE, Auchenbach MB, Javaras KN, Hess EV. Comorbidity of fibromyalgia and psychiatric disorders. Journal of Clinical Psychiatry. 2006;67(8):1219-1225.
907. Steed PA, Wexler GB. Temporomandibular disorders--traumatic etiology vs. nontraumatic etiology: a

clinical and methodological inquiry into symptomatology and treatment outcomes. Cranio. 2001 Jul;19(3):188-94.
908. Wang H, Ahrens C, Rief W, Schiltenwolf M. Influence of comorbidity with depression on interdisciplinary therapy: outcomes in patients with chronic low back pain. Arthritis Res Ther. 2010;12(5):R185. doi: 10.1186/ar3155
909. Dao TT, Reynolds WJ, Tenenbaum HC. Comorbidity between myofascial pain of the masticatory muscles and fibromyalgia. J Orofac Pain. 1997 Summer;11(3):232-41.
910. Mayer TG, Towns BL, Neblett R, Theodore BR, Gatchel RJ. Chronic widespread pain in patients with occupational spinal disorders: Prevalence, psychiatric comorbidity, and association with outcomes. Spine. 2008;33(17):1889-1897. doi: 10.1097/BRS.0b013e3181808c4e
911. White LA, Birnbaum HG, Kaltenboeck A, Tang J, Mallett D, Robinson RL. Employees with fibromyalgia: Medical comorbidity, healthcare costs, and work loss. Journal of Occupational and Environmental Medicine. 2008;50(1):13-24. doi: 10.1097/JOM.0b013e31815cff4b
912. Schuler M, Njoo N, Hestermann M, Oster P, Hauer K. Acute and chronic pain in geriatrics: clinical characteristics of pain and the influence of cognition. Pain medicine (Malden, Mass.). 2004;5(3):253-62.
913. Bazzichi L, Consensi A, Rossi A, Giacomelli C, De Feo F, Doveri M, et al. Spasmophilia comorbidity in fibromyalgia syndrome. Clin Exp Rheumatol. 2010 Nov-Dec;28(6 Suppl 63):S94-9.
914. Carbonell-Baeza A, Aparicio VA, Chillón P, Femia P, Delgado-Fernández M, Ruiz JR. Effectiveness of multidisciplinary therapy on symptomatology and quality of life in women with fibromyalgia. Clinical and Experimental Rheumatology. 2011;29(6 SUPPL. 69):S97-S103.
915. Roth T, Price JM, Amato DA, Rubens RP, Roach JM, Schnitzer TJ. The effect of eszopiclone in patients with Insomnia and coexisting rheumatoid arthritis: A pilot study. Primary care companion to the Journal of clinical psychiatry. 2009;11(6):292-301. doi: 10.4088/PCC.08m00749bro
916. Roth T, Lankford DA, Bhadra P, Whalen E, Resnick EM. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: a randomized, placebo-controlled, 2-way crossover polysomnography study. Arthritis care & research. 2012;64(4):597-606. doi: 10.1002/acr.21595
917. Huber J, Lisi?ski P, Polowczyk A. Reinvestigation of the dysfunction in neck and shoulder girdle muscles as the reason of cervicogenic headache among office workers. Disability and rehabilitation. 2013;35(10):793-802. doi: 10.3109/09638288.2012.709306
918. Tsai PF, Chang JY, Beck C, Kuo YF, Keefe FJ. A pilot cluster-randomized trial of a 20-week Tai Chi program in elders with cognitive impairment and osteoarthritic knee: effects on pain and other health outcomes. Journal of pain and symptom management. 2013;45(4):660-9. doi: 10.1016/j.jpainsymman.2012.04.009
919. Brinks A, van Rijn RM, Bohnen AM, Slee GL, Verhaar JA, Koes BW, et al. Effect of corticosteroid injection for trochanter pain syndrome: design of a randomised clinical trial in general practice. BMC musculoskeletal disorders. 2007;8:95. doi: 10.1186/1471-2474-8-95
920. Kroenke K, Bair M, Damush T, Hoke S, Nicholas G, Kempf C, et al. Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study: design and practical implications of an intervention for comorbid pain and depression. General hospital psychiatry. 2007;29(6):506-17.
921. Rosemann T, Korner T, Wensing M, Gensichen J, Muth C, Joos S, et al. Rationale, design and conduct of a comprehensive evaluation of a primary care based intervention to improve the quality of life of osteoarthritis patients. The PraxArt-project: a cluster randomized controlled trial [ISRCTN87252339]. BMC Public Health. 2005;5:77. doi: 10.1186/1471-2458-5-77
922. Zonneveld LN, van 't Spijker A, Passchier J, van Busschbach JJ, Duivenvoorden HJ. The effectiveness of a training for patients with unexplained physical symptoms: protocol of a cognitive behavioral group training and randomized controlled trial. BMC public health. 2009;9:251. doi: 10.1186/1471-2458-9-251
923. Fary RE, Carroll GJ, Briffa TG, Gupta R, Briffa NK. The effectiveness of pulsed electrical stimulation (E-PES) in the management of osteoarthritis of the knee: a protocol for a randomised controlled trial. BMC musculoskeletal disorders. 2008;9:18. doi: 10.1186/1471-2474-9-18
924. Spencer LM, Alison JA, McKeough ZJ. Do supervised weekly exercise programs maintain functional exercise capacity and quality of life, twelve months after pulmonary rehabilitation in COPD? BMC pulmonary medicine. 2007;7:7. doi: 10.1186/1471-2466-7-7
925. Coleman S, McQuade J, Rose J, Inderjeeth C, Carroll G, Briffa NK. Self-management for osteoarthritis of the knee: does mode of delivery influence outcome? BMC musculoskeletal disorders [Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2010;11:56. doi: 10.1186/1471-2474-11-56
926. Hermsen LA, Leone SS, van der Windt DA, Smalbrugge M, Dekker J, van der Horst HE. Functional outcome in older adults with joint pain and comorbidity: design of a prospective cohort study. BMC Musculoskelet Disord. 2011;12:241. doi: 10.1186/1471-2474-12-241
927. Karp JF, Rollman BL, Reynolds CF, Morse JQ, Lotrich F, Mazumdar S, et al. Addressing both depression and pain in late life: the methodology of the ADAPT study. Pain medicine (Malden, Mass.) [Randomized Controlled Trial; Research Support, N.I.H., Extramural; Research Support, U.S. Gov't, Non-P.H.S.]. 2012;13(3):405-18. doi: 10.1111/j.1526-4637.2011.01322.x

928. Llor C, Moragas A, Bayona C, Morros R, Pera H, Cots JM, et al. Effectiveness of anti-inflammatory treatment versus antibiotic therapy and placebo for patients with non-complicated acute bronchitis with purulent sputum. The BAAP Study protocol. BMC pulmonary medicine [Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. 2011;11:38. doi: 10.1186/1471-2466-11-38
929. Meems M, Oudsten B, Meems BJ, Pop V. Effectiveness of mechanical traction as a non-surgical treatment for carpal tunnel syndrome compared to care as usual: Study protocol for a randomized controlled trial. Trials. 2014;15:180. doi: 10.1186/1745-6215-15-180
930. Eytan A, Alberque C. Depression and somatic comorbidity [2]. Australian and New Zealand Journal of Psychiatry. 2001;35(5):692-693. doi: 10.1046/j.1440-1614.2001.0950c.x
931. Rozzini R, Sabatini T, Barbisoni P, Trabucchi M, De Groot V, Beckerman H, et al. How to measure comorbidity in elderly persons (multiple letters). Journal of Clinical Epidemiology. 2004;57(3):321-323. doi: 10.1016/j.jclinepi.2003.08.001
932. Leutgeb U. Comorbidity of headache, other pain and RLS: do analgesics play a part? Cephalalgia. 2009 May;29(5):591-2. doi: 10.1111/j.1468-2982.2008.01762.x
933. Thielke SM, Unutzer J. Pain is not a benign symptom among older adults: comment on Blyth et al., "pain, frailty, and comorbidity in older men: The CHAMP study". Pain. 2008 Nov 15;140(1):1-2. doi: 10.1016/j.pain.2008.09.022
934. Whitehead WE. Twin studies used to prove that the comorbidity of major depressive disorder with IBS is NOT influenced by heredity. Am J Gastroenterol. 2007 Oct;102(10):2230-1. doi: 10.1111/j.1572-0241.2007.01472.x
935. Evans R. Post-traumatic headaches: Commentary: Clinical characteristics, comorbidity, and treatment. Headache: The Journal of Head and Face Pain. 2009;49(7):1116-1119. Available from: PsycINFO. doi: 10.1111/j.1526-4610.2009.01463.x
936. Mogil JS. The etiology and symptomatology of spontaneous pain. The Journal of Pain. 2012;13(10):932-933. Available from: PsycINFO. doi: 10.1016/j.jpain.2012.07.006
937. van der Windt D. The role of co-morbidity in accumulating risk of chronic pain. Pain. 2012;153(2):259-260. Available from: PsycINFO. doi: 10.1016/j.pain.2011.10.040
938. Bible E. Pain: Comorbidity of neuropathic pain and migraine in patients with multiple sclerosis. Nat Rev Neurol. 2013 Oct;9(10):544. doi: 10.1038/nrneurol.2013.175
939. Hüppe A, Raspe H. Amplified back pain and comorbidity in the population. Amplifizierte Rückenschmerzen und Komorbidität in der Bevölkerung. 2009;23(3):275-283. doi: 10.1007/s00482-009-0783-8
940. Salmi P, Svedberg P, Hagberg J, Lundh G, Linder J, Alexanderson K. Multidisciplinary investigations recognize high prevalence of co-morbidity of psychiatric and somatic diagnoses in long-term sickness absentees. Scandinavian Journal of Public Health. 2009;37(1):35-42. doi: 10.1177/1403494808095954
941. Hurwitz EL, Morgenstern H. The effect of comorbidity on care seeking for back problems in the United States. Annals of Epidemiology. 1999;9(4):262-70. doi: 10.1016/s1047-2797(98)00059-3
942. van Dijk GM, Veenhof C, Schellevis F, Hulsmans H, Bakker JP, Arwert H, et al. Comorbidity, limitations in activities and pain in patients with osteoarthritis of the hip or knee. BMC Musculoskelet Disord. 2008;9:95. doi: 10.1186/1471-2474-9-95
943. Heo M, Pietrobelli A, Wang D, Heymsfield SB, Faith MS. Obesity and functional impairment: influence of comorbidity, joint pain, and mental health. Obesity (Silver Spring). 2010 Oct;18(10):2030-8. doi: 10.1038/oby.2009.400
944. Fernández-de-las-Peñas C, Hernández-Barrera V, Alonso-Blanco C, Palacios-Ceña D, Carrasco-Garrido P, Jiménez-Sánchez S, et al. Prevalence of neck and low back pain in community-dwelling adults in Spain: a population-based national study. Spine [Randomized Controlled Trial]. 2011;36(3):E213-9. doi: 10.1097/BRS.0b013e3181d952c2
945. Siemons L, ten Klooster PM, van de Laar MA, van den Ende CH, Hoogeboom TJ. Validity of summing painful joint sites to assess joint-pain comorbidity in hip or knee osteoarthritis. BMC Musculoskelet Disord. 2013;14:234. doi: 10.1186/1471-2474-14-234
946. Haut S, Markowitz S, Lipton RB. Comorbidity of migraine and epilepsy. In: Comorbidity in migraine.: Wiley-Blackwell; 2011 p.59-80. Available from: PsycINFO
947. Keefer L, Kiebles JL, Taft TH. Psychological co-morbidities of irritable bowel syndrome. In: Psychological co-morbidities of physical illness: A behavioral medicine perspective.: Springer Science + Business Media, New York, NY; 2011 p.385-414. Available from: PsycINFO
948. Psaros C, Israel J, O'Cleirigh C, Bedoya CA, Safren SA. Psychological co-morbidities of HIV/AIDS. In: Psychological co-morbidities of physical illness: A behavioral medicine perspective.: Springer Science + Business Media, New York, NY; 2011 p.233-273. Available from: PsycINFO
949. Radat F, Kalaydjian A, Merikangas KR. Psychiatric comorbidity in migraine. In: Comorbidity in migraine.: Wiley-Blackwell; 2011 p.1-13. Available from: PsycINFO
950. Katz J, Pagé MG, Fashler S, Rosenbloom BN, Asmundson GJG. Chronic pain and the anxiety disorders: Epidemiology, mechanisms and models of comorbidity, and treatment. In: Mental health and pain: Somatic and psychiatric components of pain in mental health.: Springer-Verlag Publishing, New York, NY; 2014 p.119-155.

Available from: PsycINFO
951. Cano A, Leonard MT, Franz A. The significant other version of the Pain Catastrophizing Scale (PCS-S): preliminary validation. Pain. 2005;119(1-3):26-37.
952. Dolan P. Modeling valuations for EuroQol health states (Brief record). Medical Care. 1997;35(11):1095-1108.
953. Zelman DC, Gore M, Dukes E, Tai KS, Brandenburg N. Validation of a modified version of the brief pain inventory for painful diabetic peripheral neuropathy. Journal of pain and symptom management. 2005;29(4):401-10.
954. Baron M, Schieir O, Hudson M, Steele R, Janelle-Montcalm A, Bernstein J, et al. Evaluation of the clinimetric properties of the Early Inflammatory Arthritis--self-administered comorbidity questionnaire. Rheumatology (Oxford). 2009 Apr;48(4):390-4. doi: 10.1093/rheumatology/ken504
955. Dersh J, Mayer T, Gatchel RJ, Towns B, Theodore B, Polatin P. Psychiatric comorbidity in chronic disabling occupational spinal disorders has minimal impact on functional restoration socioeconomic outcomes. Spine. 2007;32(17):1917-1925. doi: 10.1097/BRS.0b013e31811329ac
956. Slover JMD, Abdu WMD, Ms, Lurie J, Hanscom B, Ms, et al. 8:36 General versus spine-specific health surveys do comorbidities influence baseline results? The Spine Journal. 2002;2(5):63-63.
957. Peilot B, Andrell P, Samuelsson A, Mannheimer C, Frodi A, Sundler AJ. Time to gain trust and change--experiences of attachment and mindfulness-based cognitive therapy among patients with chronic pain and psychiatric co-morbidity. Int J Qual Stud Health Well-being. 2014;9:24420. doi: 10.3402/qhw.v9.24420
958. Kugler C, Rudofsky G. The role of comorbidity burden for patients with symptomatic peripheral arterial disease (PAD). A quantitative approach. Int Angiol. 2003 Sep;22(3):290-301.
959. Smith RN, Holland EF, Studd JW. The symptomatology of progestogen intolerance. Maturitas. 1994 Feb;18(2):87-91.
960. Leiknes KA, Finset A, Moum T, Sandanger I. "Current somatoform disorders in Norway: Prevalence, risk factors and comorbidity with anxiety, depression and muscoskeletal disorders": Erratum. Social Psychiatry and Psychiatric Epidemiology. 2007 Sep;42(9):711. Available from: PsycINFO.
961. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, et al. "Common chronic pain conditions in developed and developing countries: Gender and age differences and comorbidity with depression-anxiety disorders:" Erratum. The Journal of Pain. 2009 May;10(5):553. Available from: PsycINFO.
962. Wun YT, Chan K, Lee A. Co-morbidity in general practice. Family Practice. 1998;15(3):266-268. doi: 10.1093/fampra/15.3.266
963. Liu M, Tsuji T, Tsujiuchi K, Chino N. Comorbidities in stroke patients as assessed with a newly developed comorbidity scale. Am J Phys Med Rehabil. 1999 Sep-Oct;78(5):416-24.
964. Research, Markets. Article]. In: Research and Markets: Peripheral neuropathic pain - a common co-morbidity for HIV, diabetes, and herpes zoster: an epidemiological study from Datamonitor. 2012
965. Calandre E, Slim M, Garcia-Leiva J, Rodriguez-Lopez C, Torres P, Rico-Villademoros F. Agomelatine for the Treatment of Patients with Fibromyalgia and Depressive Symptomatology: An Uncontrolled, 12-Week, Pilot Study. Pharmacopsychiatry. 2014;47(2):67-72.
966. Traub RJ, Cao DY, Karpowicz J, Pandya S, Ji Y, Dorsey SG, et al. A clinically relevant animal model of temporomandibular disorder and irritable bowel syndrome comorbidity. J Pain. 2014 Sep;15(9):956-66. doi: 10.1016/j.jpain.2014.06.008
967. Loza E, Lajas C, Andreu J, Balsa A, González-Álvaro I, Illera O, et al. Consensus statement on a framework for the management of comorbidity and extra-articular manifestations in rheumatoid arthritis. Rheumatology International. 2015;35(3):445-458.
968. Sledjeski E, Speisman B, Dierker L. Does number of lifetime traumas explain the relationship between PTSD and chronic medical conditions? Answers from the National Comorbidity Survey-Replication (NCS-R). Journal of Behavioral Medicine. 2015 (Preprints):1-9.
969. Beurskens AJ, Bultmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. Occup Environ Med. 2000 May;57(5):353-7.
970. Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The association between chronic low back pain and sleep: a systematic review. Clin J Pain. 2011 Feb;27(2):169-81. doi: 10.1097/AJP.0b013e3181f3bdd5
971. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Varonen H, Kalso E, et al. Cardiovascular and lifestyle risk factors in lumbar radicular pain or clinically defined sciatica: a systematic review. Eur Spine J. 2007 Dec;16(12):2043-54. doi: 10.1007/s00586-007-0362-6
972. Leboeuf-Yde C. Alcohol and low-back pain: a systematic literature review. J Manipulative Physiol Ther. 2000 Jun;23(5):343-6.
973. Graham CD, Rose MR, Grunfeld EA, Kyle SD, Weinman J. A systematic review of quality of life in adults with muscle disease. J Neurol. 2011 Sep;258(9):1581-92. doi: 10.1007/s00415-011-6062-5
974. Colon-Emeric C, O'Connell MB, Haney E. Osteoporosis piece of multi-morbidity puzzle in geriatric care. Mt Sinai J Med. 2011 Jul-Aug;78(4):515-26. doi: 10.1002/msj.20269
975. Lenze EJ, Munin MC, Skidmore ER, Dew MA, Rogers JC, Whyte EM, et al. Onset of depression in elderly persons after hip fracture: implications for prevention and early intervention of late-life depression. J Am

Geriatr Soc. 2007 Jan;55(1):81-6. doi: 10.1111/j.1532-5415.2006.01017.x
976. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. Arch Intern Med. 2007 Jan 22;167(2):188-94. doi: 10.1001/archinte.167.2.188
977. Ferreira BI, Abreu JL, Reis JP, Figueiredo AM. Psoriasis and Associated Psychiatric Disorders: A Systematic Review on Etiopathogenesis and Clinical Correlation. J Clin Aesthet Dermatol. 2016 Jun;9(6):36-43.
978. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 2009 Jul-Aug;7(4):357-63. doi: 10.1370/afm.983
979. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010 May;62(5):600-10. doi: 10.1002/acr.20140
980. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990 Feb;33(2):160-72.
981. Choy EH, Arnold LM, Clauw DJ, Crofford LJ, Glass JM, Simon LS, et al. Content and criterion validity of the preliminary core dataset for clinical trials in fibromyalgia syndrome. J Rheumatol. 2009 Oct;36(10):2330-4. doi: 10.3899/jrheum.090368
982. Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, et al. Fibromyalgia syndrome module at OMERACT 9: domain construct. J Rheumatol. 2009 Oct;36(10):2318-29. doi: 10.3899/jrheum.090367
983. Riddle DL, Stratford PW, Singh JA, Strand CV. Variation in outcome measures in hip and knee arthroplasty clinical trials: a proposed approach to achieving consensus. J Rheumatol. 2009 Sep;36(9):2050-6. doi: 10.3899/jrheum090356
984. Loney PL, Chambers LW, Bennett KJ, Roberts JG, Stratford PW. Critical appraisal of the health research literature: prevalence or incidence of a health problem. Chronic Dis Can. 1998;19(4):170-6.
985. AMSTAR. Assessing the Methodological Quality of Systematic Reviews THE DEVELOPMENT OF AMSTAR. [cited 2015 20/06/2015]. Available from: http://amstar.ca/Existing_Critical_Appraisal_Tools.php
986. Ahmed S, Shahid RK, Leis A, Haider K, Kanthan S, Reeder B, et al. Should noncurative resection of the primary tumour be performed in patients with stage iv colorectal cancer? A systematic review and meta-analysis. Curr Oncol. 2013 Oct;20(5):e420-41. doi: 10.3747/co.20.1469
987. Shamliyan T, Kane RL, Dickinson S. A systematic review of tools used to assess the quality of observational studies that examine incidence or prevalence and risk factors for diseases. J Clin Epidemiol. 2010 Oct;63(10):1061-70. doi: 10.1016/j.jclinepi.2010.04.014
988. Ablin JN, Buskila D. Personalized treatment of pain. Curr Rheumatol Rep. 2013 Jan;15(1):298. doi: 10.1007/s11926-012-0298-7
989. Dawes M. Co-morbidity: we need a guideline for each patient not a guideline for each disease. Fam Pract. 2010 Feb;27(1):1-2. doi: 10.1093/fampra/cmp106
990. Lugtenberg M, Burgers JS, Clancy C, Westert GP, Schneider EC. Current guidelines have limited applicability to patients with comorbid conditions: a systematic analysis of evidence-based guidelines. PLoS One. 2011;6(10):e25987. doi: 10.1371/journal.pone.0025987
991. New South Wales Department of Health. NSW Clinical Guidelines for the Care of Persons with Comorbid Mental Illness and Substance Abuse Disorders in Acute Care Settings. NSW Department of Health; 2009.
992. Mills KL, Drug N, Centre AR. Guidelines on the Management of Co-occurring Alcohol and Other Drug and Mental Health Conditions in Alcohol and Other Drug Treatment Settings. National Drug & Alcohol Research Centre; 2009.
993. Rattray J, Jones MC. Essential elements of questionnaire design and development. J Clin Nurs. 2007 Feb;16(2):234-43. doi: 10.1111/j.1365-2702.2006.01573.x
994. Hinkin TR, Tracey JB, Enz CA. Scale Construction: Developing Reliable and Valid Measurement Instruments. Journal of Hospitality & Tourism Research. 1997 February 1, 1997;21(1):100-120. doi: 10.1177/109634809702100108
995. Letrait M, Lurie A, Bean K, Mesbah M, Venot A, Strauch G, et al. The Asthma Impact Record (AIR) index: a rating scale to evaluate the quality of life of asthmatic patients in France. Eur Respir J. 1996 Jun;9(6):1167-73.
996. Matthews TD, Kostelis KT. Designing and Conducting Research in Health and Human Performance. Hoboken: Wiley; 2011.
997. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007 Jan;60(1):34-42. doi: 10.1016/j.jclinepi.2006.03.012
998. Cuhls K. Delphi method. [updated 12/11/2015]. 93-113. Available from: www.unido.org/fileadmin/import/16959_DelphiMethod.pdf
999. Skulmoski GJ, Hartman FT, Krahn J. The Delphi Method for Graduate Research. Journal of Information Technology Education. 2007;6:1-21.
1000. Streiner D, Norman G. Health measurement scales: a practical guide to their development and use. 4th

ed: Oxford University Press; 2008.
1001. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ. 1993 May 29;306(6890):1437-40.
1002. Steer RA, Rissmiller DJ, Beck AT. Use of the Beck Depression Inventory-II with depressed geriatric inpatients. Behav Res Ther. 2000 Mar;38(3):311-8.
1003. Beck A, Steer R, Brown G. Beck Depression Inventory. [cited 2015 13/11/2015]. Available from: http://academicdepartments.musc.edu/family_medicine/rcmar/beck.htm
1004. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961 Jun;4:561-71.
1005. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996 Dec;67(3):588-97. doi: 10.1207/s15327752jpa6703_13
1006. Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S454-66. doi: 10.1002/acr.20556
1007. Ware JE, Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000 Dec 15;25(24):3130-9.
1008. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. Spine (Phila Pa 1976). 1983 Mar;8(2):141-4.
1009. Smeets R, Koke A, Lin CW, Ferreira M, Demoulin C. Measures of function in low back pain/disorders: Low Back Pain Rating Scale (LBPRS), Oswestry Disability Index (ODI), Progressive Isoinertial Lifting Evaluation (PILE), Quebec Back Pain Disability Scale (QBPDS), and Roland-Morris Disability Questionnaire (RDQ). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S158-73. doi: 10.1002/acr.20542
1010. Weiss NA. Chi-Square Homogeneity Test. In: Introductory statistics. 9th ed: Pearson, Addison-Wesley; 2012 p.613-621.
1011. Field A. Discovering Statistics Using SPSS. 3rd ed: SAGE Publications; 2009.
1012. Goldberg LR. The structure of personality traits: vertical and horizontal aspects. In: Funder DC, Parke RD, Tomlinson-Keasey C, Widaman K, editors. Studying lives through time: Personality and development. Washington DC: American Psychology Association; 1993 p.169-188.
1013. Stevens J, Stevens Ja. What loadings Should Be Used for Interpretation? In: Applied multivariate statistics for the social sciences. 5th ed. ed. New York: Routledge; 2009 p.332.
1014. Hair JF, Anderson RE. Multivariate data analysis. Prentice Hall Higher Education; 2010.
1015. Fanciullo GJ, Hanscom B, Weinstein JN, Chawarski MC, Jamison RN, Baird JC. Cluster analysis classification of SF-36 profiles for patients with spinal pain. Spine (Phila Pa 1976). 2003 Oct 1;28(19):2276-82. doi: 10.1097/01.BRS.0000084880.33281.EB
1016. Gold JE, Piligian G, Glutting JJ, Hanlon A, Frings-Dresen MH, Sluiter JK. Cluster analysis of symptoms among patients with upper extremity musculoskeletal disorders. J Occup Rehabil. 2010 Dec;20(4):526-36. doi: 10.1007/s10926-010-9240-x
1017. Markham S. Analysis of Variance (ANOVA). Monash University; 2001. Available from: http://www.csse.monash.edu.au/~smarkham/resources/anova.htm
1018. Lin J-D, Lin J-S, Chen L-L, Chang C-H, Huang Y-C, Su Y-C. BCQs: A Body Constitution Questionnaire to assess Stasis in traditional Chinese medicine. European Journal of Integrative Medicine. 2012;4(4):e379-e391. doi: 10.1016/j.eujim.2012.05.001
1019. Zhu W. Chinese medicine diagnosis [中医诊断学]. 1st ed. Beijing: People's medical publishing house Co. Ltd; 1999.
1020. Maciocia G. The Practice of Chinese Medicine The Treatment of Diseases with Acupuncture and Chinese Herbs. 2nd ed. Philadelphia: Churchill Livingstone Elsevier; 2008.
1021. Maclean W, Lyttleton J. CLINICAL HANDBOOK OF INTERNAL MEDICINE The Treatment of Disease with Traditional Chinese Medicine. 1st ed: University of Western Sydney Macarthur; 1998.
1022. Shi Q, Wang H. Orthopaedics and traumatology [骨伤科学]. 1st ed. 北京: People medical publishing house [人民卫生出版社]; 2001. p. 2155.
1023. Task Force on Taxonomy of the International Association for the Study of Pain. CLASSIFICATION OF CHRONIC PAIN - DESCRIPTIONS OF CHRONIC PAIN SYNDROMES AND DEFINITIONS OF PAIN TERMS. 2nd ed1994 [Available from: www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Classification-of-Chronic-Pain.pdf
1024. Melzack R, Katz J, Jeans ME. The role of compensation in chronic pain: analysis using a new method of scoring the McGill Pain Questionnaire. Pain. 1985 Oct;23(2):101-12.
1025. Yao NL. Differential diagnosis of symptom in Chinese medicine [中医症状鉴别诊断学]. 2nd ed: People Health Publishing House [人民卫生出版社]; 1984.
1026. Luo YQ. Chinese medicine gynaecology [中医妇科学]. 1st ed: Shanghai Science and Technology Press; 1986.
1027. Gu B. Chinese medicine surgery [中医外科学]. 1st ed. Shanghai: Shanghai Science Technology Press;

1986.
1028. Grant SJ, Schnyer RN, Chang DH, Fahey P, Bensoussan A. Interrater reliability of chinese medicine diagnosis in people with prediabetes. Evid Based Complement Alternat Med. 2013;2013:710892. doi: 10.1155/2013/710892
1029. Kang BK, Park TY, Lee JA, Moon TW, Ko MM, Choi J, et al. Reliability and validity of the Korean Standard Pattern Identification for Stroke (K-SPI-Stroke) questionnaire. BMC Complement Altern Med. 2012;12:55. doi: 10.1186/1472-6882-12-55
1030. Lohr KN, Aaronson NK, Alonso J, Burnam MA, Patrick DL, Perrin EB, et al. Evaluating quality-of-life and health status instruments: development of scientific review criteria. Clin Ther. 1996 Sep-Oct;18(5):979-92.
1031. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res. 1995 Aug;4(4):293-307.
1032. Yan Y. Sun exposure behaviors and risk of superficial spreading and nodular melanoma [Master's thesis]: Southern California; 2006.
1033. Twycross RG. Opioids. In: Wall PD, Melzack R, editors. Textbook Of Pain. Edinburgh: Churchill Livingstone; 1999.
1034. Harden RN, Weinland SR, Remble TA, Houle TT, Colio S, Steedman S, et al. Medication Quantification Scale Version III: update in medication classes and revised detriment weights by survey of American Pain Society Physicians. J Pain. 2005 Jun;6(6):364-71. doi: 10.1016/j.jpain.2005.01.350
1035. Bland JM, Altman DG. Statistics notes: Cronbach's alpha. BMJ. 1997;314(7080):572. doi: 10.1136/bmj.314.7080.572
1036. National Institutes of Health. Menopause. 2008 [cited 2013 13/07/2013]. Available from: http://www.nia.nih.gov/health/publication/menopause
1037. Park YJ, Park JS, Kim MY, Park YB. Development of a valid and reliable phlegm pattern questionnaire. J Altern Complement Med. 2011 Sep;17(9):851-8. doi: 10.1089/acm.2010.0504
1038. Zhao H, Xiong WH, Zhao X, Wang LM, Chen JX. Development and evaluation of a traditional Chinese medicine syndrome questionnaire for measuring sub-optimal health status in China. J Tradit Chin Med. 2012 Jun;32(2):129-36.
1039. Lee S, Park J, Lee H, Kim K. Development and validation of Yin-Deficiency Questionnaire. Am J Chin Med. 2007;35(1):11-20. doi: 10.1142/S0192415X07004576
1040. Tavakol M, Dennick R. Making sense of Cronbach's alpha. Int J Med Educ. 2011 Jun 27;2:53-55. doi: 10.5116/ijme.4dfb.8dfd
1041. Ismail AI, Belli RF, Sohn W, Toussaint L. Internal consistency and reliability of a questionnaire assessing organizational innovation in two schools of dentistry. J Dent Educ. 2002 Apr;66(4):469-77.
1042. Reise SP, Waller NG, Comrey AL. Factor analysis and scale revision. Psychol Assess. 2000 Sep;12(3):287-97.
1043. Wang XN, Zhou V, Liu Q, Gao Y, Zhou XH. Evaluation of the accuracy of diagnostic scales for a syndrome in Chinese medicine in the absence of a gold standard. Chin Med. 2016;11:35. doi: 10.1186/s13020-016-0100-2
1044. Kohn MA, Carpenter CR, Newman TB. Understanding the direction of bias in studies of diagnostic test accuracy. Acad Emerg Med. 2013 Nov;20(11):1194-206. doi: 10.1111/acem.12255
1045. Sun Y, Liu P, Zhao Y, Jia L, He Y, Xue SA, et al. Characteristics of TCM constitutions of adult Chinese women in Hong Kong and identification of related influencing factors: a cross-sectional survey. J Transl Med. 2014;12:140. doi: 10.1186/1479-5876-12-140
1046. Zhang W, Cao JT, Liu HY. [Effects of pathogenic wind-dampness on lung tissue cytokines in rats with syndrome due to pathogenic cold invading lung]. Zhong Xi Yi Jie He Xue Bao. 2008 Jul;6(7):748-51. doi: 10.3736/jcim20080717
1047. MacCallum RC, Widaman KF, Zhang S, Hong S. Sample Size in Factor Analysis. Psychological Methods. 1999;4(1):84-99. doi: 10.1037/1082-989X.4.1.84
1048. LeResche L. Gender considerations in the epidemiology of chronic pain. In: Crombie IK, Croft PR, Linton SJ, Leresche L, Von Korff M, editors. Epidemiology of Pain: A Report of the Task Force on Epidemiology of the International Association for the Study of Pain. 1st ed: IASP Press; 1999 p.43-52.
1049. Aliyev R, Vieth T, Geiger G. Traditional Chinese medicine in diagnosis and treatment of fibromyalgia syndrome. Georgian Med News. 2010 Nov (188):38-45.
1050. Huang H, Chai S, Huang H, Chen X. Cluster Analysis of Syndrome Patterns of Osteoporosis in Traditional Chinese Medicine Joumal of Guangzhou University of Traditional Chinese Medicine. 2007;24(3):180-185.
1051. Billis E, McCarthy CJ, Roberts C, Gliatis J, Papandreou M, Gioftsos G, et al. Sub-grouping patients with non-specific low back pain based on cluster analysis of discriminatory clinical items. J Rehabil Med. 2013 Feb;45(2):177-85. doi: 10.2340/16501977-1100
1052. Gu WL, Shi ZX, Yu YX, Wu YW, Lu BW, Hui KK. [Distribution characteristics of syndrome types in essential hypertension]. Zhong Xi Yi Jie He Xue Bao. 2010 Sep;8(9):842-7. doi: 10.3736/jcim20100907
1053. Fan XF, Deng YQ, Wu GL. [Study on the distribution and characteristics of Chinese medicine syndrome

in patients with nonalcoholic fatty liver disease]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2011 Oct;31(10):1332-6.
1054. Zhang BY. Chinese Medical Internal Medicine [中医内科]. Beijing: People's Medical Publishing House; 1988.
1055. Costello AB, Osborne JW. Best Practices in Exploratory Factor Analysis: Four Recommendations for Getting the Most From Your Analysis. Practical Assessment Research & Evaluation. 2005;10(7):1-9. doi: 10.1.1.110.9154
1056. Gelasakis AI, Valergakis GE, Arsenos G, Banos G. Description and typology of intensive Chios dairy sheep farms in Greece. Journal of Dairy Science. 2012;95(6):3070-9. doi: 10.3168/jds.2011-4975
1057. Yong AG, Pearce S. A Beginner's Guide to Factor Analysis: Focusing on Exploratory Factor Analysis. Tutorials in Quantitative Methods for Psychology. 2013;9(2):79-94. doi: 10.20982/tqmp.09.2.p079
1058. Vogt W, Nagel D. Cluster analysis in diagnosis. Clin Chem. 1992 Feb;38(2):182-98.
1059. Plazier M, Ost J, Stassijns G, De Ridder D, Vanneste S. Pain characteristics in fibromyalgia: understanding the multiple dimensions of pain. Clin Rheumatol. 2015 Apr;34(4):775-83. doi: 10.1007/s10067-014-2736-6
1060. Wei HF, Liu T, Xing LJ, Zheng PY, Ji G. [Distribution pattern of traditional Chinese medicine syndromes in 793 patients with fatty liver disease]. Zhong Xi Yi Jie He Xue Bao. 2009 May;7(5):411-7. doi: 10.3736/jcim20090503
1061. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11(2S):S105-20.
1062. Parvaresh N, Sabahi AR, Mazhari S, Gilani H. A Study of the Sexual Function, Sleep, and Weight Status of Patients after 6 Months of Methadone Maintenance Treatment. Addict Health. 2015 Winter-Spring;7(1-2):24-9.
1063. Cheshire WP, Fealey RD. Drug-induced hyperhidrosis and hypohidrosis: incidence, prevention and management. Drug Saf. 2008;31(2):109-26.
1064. Bensky D, Clavey S, Gamble A, Stöger E, Bensky LL. Chinese herbal medicine : materia medica. 3rd ed: Eastland Press, Inc.; 2004.
1065. MacPherson H, Thorpe L, Thomas K, Campbell M. Acupuncture for low back pain: traditional diagnosis and treatment of 148 patients in a clinical trial. Complement Ther Med. 2004 Mar;12(1):38-44. doi: 10.1016/S0965-2299(03)00125-0
1066. Berle C, Cobbin D, Smith N, Zaslawski C. An innovative method to accommodate Chinese medicine pattern diagnosis within the framework of evidence-based medical research. Chin J Integr Med. 2011 Nov;17(11):824-33. doi: 10.1007/s11655-011-0893-x
1067. ZHOU J-x, YU G-y, NIE Y-y, TANG M, LI J. Chinese Medicine Syndrome Characteristic Based on Clustering Analysis of 2 029 Cases of Angina Pectoris of Coronary Heart Disease Chinese Journal of Information on TCM. 2011;18(8):19-23.
1068. Lu C, Niu X, Xiao C, Chen G, Zha Q, Guo H, et al. Network-based gene expression biomarkers for cold and heat patterns of rheumatoid arthritis in traditional chinese medicine. Evid Based Complement Alternat Med. 2012;2012:203043. doi: 10.1155/2012/203043
1069. Lu C, Xiao C, Chen G, Jiang M, Zha Q, Yan X, et al. Cold and heat pattern of rheumatoid arthritis in traditional Chinese medicine: distinct molecular signatures indentified by microarray expression profiles in CD4-positive T cell. Rheumatol Int. 2012 Jan;32(1):61-8. doi: 10.1007/s00296-010-1546-7
1070. Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. Eur Spine J. 2006 Jun;15(6):834-48. doi: 10.1007/s00586-004-0864-4
1071. Dawson J, Linsell L, Zondervan K, Rose P, Randall T, Carr A, et al. Epidemiology of hip and knee pain and its impact on overall health status in older adults. Rheumatology (Oxford). 2004 Apr;43(4):497-504. doi: 10.1093/rheumatology/keh086
1072. Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. Priority Medicines for Europe and the World 2013 Update 2013 [cited 26/08/2015]. Available from: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1
1073. WHO. WHO's cancer pain ladder for adults. [19/06/2014]. Available from: http://www.who.int/cancer/palliative/painladder/en/
1074. Blyth FM, March LM, Cousins MJ. Chronic pain-related disability and use of analgesia and health services in a Sydney community. Med J Aust. 2003 Jul 21;179(2):84-7.
1075. de Winter JC, Dodou D, Wieringa PA. Exploratory Factor Analysis With Small Sample Sizes. Multivariate Behav Res. 2009 Mar-Apr;44(2):147-81. doi: 10.1080/00273170902794206
1076. Khamba B, Aucoin M, Lytle M, Vermani M, Maldonado A, Iorio C, et al. Efficacy of Acupuncture Treatment of Sexual Dysfunction Secondary to Antidepressants. J Altern Complement Med. 2013 Jun 21;19(11):862-. doi: 10.1089/acm.2012.0751
1077. Deng JJ, Fan HM, Zhang AM, Xie M, Tan XH. [Efficacy controlled observation on acupuncture and western medicine for gastrointestinal dysmotility in liver cirrhosis]. Zhongguo Zhen Jiu. 2013 May;33(5):389-93.

1078. Lundeberg T, Lund I. Did 'The Princess on the Pea' suffer from fibromyalgia syndrome? The influence on sleep and the effects of acupuncture. Acupunct Med. 2007 Dec;25(4):184-97.
1079. Guo RX. The effect of Electro-Acupuncture on Reducing Opioid Consumption in Patients with Chronic Pain: A Randomised Controlled Clinical Trial [Master's thesis] thesis]. [Bundoora]: RMIT University; 2006.
1080. NCCS Statistical Software. Cochran's Q Test NCCS Statistical Software [cited 2016 15/11/2016]. Available from: https://ncss-wpengine.netdna-ssl.com/wp-content/themes/ncss/pdf/Procedures/NCSS/Cochrans_Q_Test.pdf
1081. Chinese Medicine Board of Australia. Patient records guidelines. [cited 2015 15/09/2015]. Available from: http://www.chinesemedicineboard.gov.au/documents/default.aspx?record=WD12%2f8626&dbid=AP&chksum=EhgQbJNV4K6PQBnN8TulYw%3d%3d
1082. Suvinen TI, Reade PC, Hanes KR, Kononen M, Kemppainen P. Temporomandibular disorder subtypes according to self-reported physical and psychosocial variables in female patients: a re-evaluation. J Oral Rehabil. 2005 Mar;32(3):166-73. doi: 10.1111/j.1365-2842.2004.01432.x
1083. Hao X. Development of Chinese Medicine Headache Questionnaire for Tension-type Headache [PhD's thesis] thesis]. [Bundoora]: RMIT University; 2015. Available from: https://researchbank.rmit.edu.au/eserv/rmit:161473/Hao.pdf
1084. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. Cephalalgia. 1999 Mar;19(2):107-14; discussion 74.
1085. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983 Dec;24(4):385-96.
1086. Luo CM, Song YL, Huang LH, Liu CY, Chen IJ, Hsu CH. The correlation of lab data, hormone peptides, quality of life, and different traditional chinese medicine syndrome groups in type 2 diabetes patients. J Tradit Complement Med. 2013 Apr;3(2):126-33. doi: 10.4103/2225-4110.110409
1087. Song YL, Lien CY, Chiu JP, Luo CM, Liu CY, Chen IJ, et al. Relationship between Obesity-related Hormone Peptides and Quality of Life in Obese Women among Different Traditional Chinese Medicine Syndrome Groups. J Tradit Complement Med. 2012 Jan;2(1):61-6.
1088. Schedule 8 permits and notifications. Victoria State Government [cited 2016 17/11/2016]. Available from: https://www2.health.vic.gov.au/public-health/drugs-and-poisons/treatment-approvals/schedule-8-permits-and-notifications
1089. Padela AI, Schneider SM, He H, Ali Z, Richardson TM. Patient choice of provider type in the emergency department: perceptions and factors relating to accommodation of requests for care providers. Emerg Med J. 2010 Jun;27(6):465-9. doi: 10.1136/emj.2008.070383
1090. Wilson JK, Brodsky SL, Neal TMS, Cramer RJ. Prosecutor Pretrial Attitudes and Plea-Bargaining Behavior Toward Veterans With Posttraumatic Stress Disorder. Psychological Services. 2011;8(4):319-331. doi: 10.1037/a0025330
1091. Enders CK. Listwise deletion. In: Applied Missing Data Analysis: Guilford Press; 2010 p.39-40.
1092. Freedman D, Pisani R, Purves R. Statistics. 4th ed. New York: W.W. Norton & Co.; 2007.
1093. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. J Pain. 2009 Mar;10(3):316-22. doi: 10.1016/j.jpain.2008.10.003
1094. Agarwal-Kozlowski K, Lange AC, Beck H. Contact-free infrared thermography for assessing effects during acupuncture: a randomized, single-blinded, placebo-controlled crossover clinical trial. Anesthesiology. 2009 Sep;111(3):632-9. doi: 10.1097/ALN.0b013e3181b31e24
1095. Adler MW, Geller EB, Rosow CE, Cochin J. The opioid system and temperature regulation. Annu Rev Pharmacol Toxicol. 1988;28:429-49. doi: 10.1146/annurev.pa.28.040188.002241
1096. Hooten WM, Warner DO. Varenicline for opioid withdrawal in patients with chronic pain: a randomized, single-blinded, placebo controlled pilot trial. Addict Behav. 2015 Mar;42:69-72. doi: 10.1016/j.addbeh.2014.11.007
1097. Younger J, Barelka P, Carroll I, Kaplan K, Chu L, Prasad R, et al. Reduced cold pain tolerance in chronic pain patients following opioid detoxification. Pain Med. 2008 Nov;9(8):1158-63. doi: 10.1111/j.1526-4637.2008.00475.x
1098. Li X, Wu YG, Zhang HY, Shao CR. [Typing of bronchiectasis according to syndrome differentiation]. Zhong Xi Yi Jie He Xue Bao. 2004 Jul;2(4):255-7.
1099. Beeckmans N, Vermeersch A, Lysens R, Van Wambeke P, Goossens N, Thys T, et al. The presence of respiratory disorders in individuals with low back pain: A systematic review. Man Ther. 2016 Jul 25;26:77-86. doi: 10.1016/j.math.2016.07.011
1100. Gu Y, Lu C, Zha Q, Kong H, Lu X, Lu A, et al. Plasma metabonomics study of rheumatoid arthritis and its Chinese medicine subtypes by using liquid chromatography and gas chromatography coupled with mass spectrometry. Mol Biosyst. 2012 Apr;8(5):1535-43. doi: 10.1039/c2mb25022e
1101. Guo H, Niu X, Gu Y, Lu C, Xiao C, Yue K, et al. Differential Amino Acid, Carbohydrate and Lipid

Metabolism Perpetuations Involved in a Subtype of Rheumatoid Arthritis with Chinese Medicine Cold Pattern. Int J Mol Sci. 2016 Oct 21;17(10):1757. doi: 10.3390/ijms17101757
1102. Hu J. How to differentiate and treat Bi-syndrome by acupuncture and moxibustion? J Tradit Chin Med. 2002 Mar;22(1):73-6.
1103. Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. Lancet. 1997 Aug 2;350(9074):326-9. doi: 10.1016/S0140-6736(97)02419-7
1104. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012 Apr;28(2):138-44. doi: 10.1017/S0266462312000086
1105. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013 May;14(5):365-76. doi: 10.1038/nrn3475
1106. Department of Health & Human Services. Schedule 8 permits and notifications [cited 2016 24/12/2016]. Available from: https://www2.health.vic.gov.au/public-health/drugs-and-poisons/treatment-approvals/schedule-8-permits-and-notifications
1107. Chen MR, Zhang JL. Liver and gallbladder diseases [肝胆病学]. 1st ed: Shan Xi Science and Technology Press [山西科学技术出版社]; 1997.
1108. Brinkhaus B, Witt CM, Jena S, Linde K, Streng A, Irnich D, et al. Interventions and physician characteristics in a randomized multicenter trial of acupuncture in patients with low-back pain. J Altern Complement Med. 2006 Sep;12(7):649-57. doi: 10.1089/acm.2006.12.649
1109. Brinkhaus B, Witt CM, Jena S, Linde K, Streng A, Wagenpfeil S, et al. Acupuncture in patients with chronic low back pain: a randomized controlled trial. Arch Intern Med. 2006 Feb 27;166(4):450-7. doi: 10.1001/archinte.166.4.450
1110. Cherkin DC, Sherman KJ, Avins AL, Erro JH, Ichikawa L, Barlow WE, et al. A randomized trial comparing acupuncture, simulated acupuncture, and usual care for chronic low back pain. Arch Intern Med. 2009 May 11;169(9):858-66. doi: 10.1001/archinternmed.2009.65
1111. Bannister GC, Wallace WA, Stableforth PG, Hutson MA. The management of acute acromioclavicular dislocation. A randomised prospective controlled trial. J Bone Joint Surg Br. 1989 Nov;71(5):848-50.
1112. Imatani RJ, Hanlon JJ, Cady GW. Acute, complete acromioclavicular separation. J Bone Joint Surg Am. 1975 Apr;57(3):328-32.
1113. Larsen E, Bjerg-Nielsen A, Christensen P. Conservative or surgical treatment of acromioclavicular dislocation. A prospective, controlled, randomized study. J Bone Joint Surg Am. 1986 Apr;68(4):552-5.
1114. Gerritsen AA, de Vet HC, Scholten RJ, Bertelsmann FW, de Krom MC, Bouter LM. Splinting vs surgery in the treatment of carpal tunnel syndrome: a randomized controlled trial. JAMA. 2002 Sep 11;288(10):1245-51.
1115. Hui AC, Wong S, Leung CH, Tong P, Mok V, Poon D, et al. A randomized controlled trial of surgery vs steroid injection for carpal tunnel syndrome. Neurology. 2005 Jun 28;64(12):2074-8. doi: 10.1212/01.wnl.0000169017.79374.93
1116. Sachs RA, Stone ML, Devine S. Open vs. arthroscopic acromioplasty: a prospective, randomized study. Arthroscopy. 1994 Jun;10(3):248-54.
1117. Spangehl MJ, Hawkins RH, McCormack RG, Loomer RL. Arthroscopic versus open acromioplasty: A prospective, randomized, blinded study. Journal of Shoulder and Elbow Surgery. 2002;11(2):101-107. doi: 10.1067/mse.2002.120915
1118. Iversen T, Reikeras O, Solem OI. Acromioplasty for the chronic imingement syndrome [Acromionreseksjon for inneklemmingssyndrom i skulderen. Resultater etter åpen og perkutan operasjonsmetode]. Tidsskrift for den Norske Laegeforening. 1996;116(16):1879-1882.
1119. Boehm TD, Werner A, Radtke S, Mueller T, Kirschner S, Gohlke F. The effect of suture materials and techniques on the outcome of repair of the rotator cuff: a prospective, randomised study. J Bone Joint Surg Br. 2005 Jun;87(6):819-23. doi: 10.1302/0301-620X.87B6.15638
1120. Ingvarsson T, Hagglund G, Johnsson R. Anterior acromioplasty. A comparison of two techniques. Int Orthop. 1996;20(5):290-2.
1121. Nozawa S, Shimizu K, Miyamoto K, Tanaka M. Repair of pars interarticularis defect by segmental wire fixation in young athletes with spondylolysis. Am J Sports Med. 2003 May-Jun;31(3):359-64.
1122. Reitman CA, Esses SI. Direct repair of spondylolytic defects in young competitive athletes. Spine J. 2002;2(2):142-4.
1123. Songer MN, Rovin R. Repair of the pars interarticularis defect with a cable-screw construct. A preliminary report. Spine (Phila Pa 1976). 1998 Jan 15;23(2):263-9.
1124. Ranawat VS, Dowell JK, Heywood-Waddington MB. Stress fractures of the lumbar pars interarticularis in athletes: a review based on long-term results of 18 professional cricketers. Injury. 2003 Dec;34(12):915-9.
1125. Debnath UK, Freeman BJ, Gregory P, de la Harpe D, Kerslake RW, Webb JK. Clinical outcome and

return to sport after the surgical treatment of spondylolysis in young athletes. J Bone Joint Surg Br. 2003 Mar;85(2):244-9.
1126. Ivanic GM, Pink TP, Achatz W, Ward JC, Homann NC, May M. Direct stabilization of lumbar spondylolysis with a hook screw: mean 11-year follow-up period for 113 patients. Spine (Phila Pa 1976). 2003 Feb 1;28(3):255-9. doi: 10.1097/01.BRS.0000042251.62696.A5
1127. Johnson GV, Thompson AG. The Scott wiring technique for direct repair of lumbar spondylolysis. J Bone Joint Surg Br. 1992 May;74(3):426-30.
1128. Bhagia SM, Slipman CW, Nirschl M, Isaac Z, El-Abd O, Sharps LS, et al. Side effects and complications after percutaneous disc decompression using coblation technology. Am J Phys Med Rehabil. 2006 Jan;85(1):6-13.

Appendices

Appendix 1 Description of different reviews on surgery for musculoskeletal pain

Study	Included studies	Included participants	Condition/disease	Intervention	Comparison group	Follow up	Conclusion	Comment
Tamaoki et al. [89]	3	174	Acromioclavicular dislocation of shoulder	Fixation of acromioclavicular joint	Arm support with a sling	One year	There is insufficient evidence to recommend surgery for acromioclavicular dislocation.	There were fixation failures in the three trials. Two trials reporter surgery significantly delayed return to work.
Verdugo et al. [85]	4	317	Carpal tunnel syndrome	Surgery	Splinting	3/6/12 months	Surgery is better than splinting for carpal tunnel syndrome	Incidence of complication is significantly higher than splinting (RR: 1.38, 95% CI 1.08 - 1.76)
Coghlan et al. [90]	14	829	Rotator cuff disease	Open or arthroscopic subacromial decompression, arthroscopic decompression	active non operative treatment (exercise programme, physiotherapy regimen of	The follow up times were not unified and each trial was described	Due to heterogeneity amongst trials, no firm conclusion is drawn on the effectiveness or safety of surgery for rotator cuff diseases. There is silver	

Study	Included studies	Included participants	Condition/disease	Intervention	Comparison group	Follow up	Conclusion	Comment
					exercise and education, or graded physiotherapy strengthening program)	by its defined follow up times.	evidence* for no difference between open/arthroscopic subacromial decompression and active non-operative treatment for impingement and a silver evidence for no difference between arthroscopic and open subacromial decompression.	
Jacobs et al. [87]	16	1581	Sciatica due to disc herniation	Open discectomy	Other types of minimal invasive discectomy	No defined follow up time in the SR. Each study has its own follow up time.	The author concluded the effectiveness of open discectomy and other types of minimal invasive discectomy could not be confirmed when compared to each other due to the limited amount and quality evidence.	
Drazin et al. [86]	18	84 athletes and 279 non-athletes	Symptomatic spondylolysis	Surgery	No comparison group.	Not described by all studies except for one who had a mean follow up	Acceptable results are seen with the repair techniques. Ideal patients is less than 20 years old with minimal or no listhesis and no degenerative changes of the disc.	Limitation in sports is expected 5-12 months after surgery.

Study	Included studies	Included participants	Condition/disease	Intervention	Comparison group	Follow up	Conclusion	Comment
						time of 10.9 years.		
Manchikanti et al. [88]	5	336	Disc protrusion and disc decompression	Nucleoplasty	Observational studies with no comparison group	Minimal 12 months follow up was required.	There is level II-3 evidence ("evidence obtained from multiple time series with or without the intervention" [88].) for mechanical lumbar percutaneous disc decompression with nucleoplasty in treatment of leg pain.	

* Silver evidence indicated the included studies did not meet all the following four criteria:
1.Sample sizes of at least 50 per group. If the studies did not find a statistically significant difference, the studies are adequately powered for a 20% relative difference in the relevant outcome.
2. Blinding of patients and assessors for outcomes.
3. Handling of withdrawals> 80% follow up (imputations based on methods such as Last Observation Carried Forward acceptable.)
4. Concealment of allocation.
Silver ranking would also include evidence from at least one study of nonrandomised cohorts who did or did not receive therapy or evidence from at least one high quality case-control study. A randomised trial with a "head to head" comparison of agents is considered silver ranking unless a reference is provided to a comparison of one of the agents to placebo showing at least a 20% relative difference (description extracted from Coghlan et al. [90]).
CI: Confidence interval
SR: Systematic review

Appendix 2 Reported complications of surgery

Study	Complications
Tamaoki et al. [89]	Surgery for acromioclavicular dislocation (n=27) [1111]: coracoclavicular screw cut out of the clavicle (7.4%), and coracoclavicular screw broke (3.7%). Surgery for complete acromioclavicular separation (n=11) [1112]: screw pull-out that occurred within 48 hours of surgery (13.3%). Phemister procedure (n=41) [1113]: superficial infection (n=6) (14.6%), five of these being associated with migration of smooth Kirschner wires, wire breakage across the acromioclavicular joint (n=16) (39.0%) with 12 of them had errors in surgical technique (29.3%).
Verdugo et al. [85]	Carpal tunnel surgery (n=87) [1114]: painful or hypertrophic scar (60.9%); stiffness of wrist, hand, or fingers (27.6%), skin irritation (21.8%), wound haematoma (11.5%), wound infection (5.7%); severe pillar pain (2.3%), and reflex sympathetic dystrophy (1.1%). Open carpal tunnel release surgery (n=25) [1115]: mild to moderate wound pain (36%), wound haematomas (8%).
Coghlan et al. [90]	Open subacromial decompression (n=2) [1116]: 5% Superficial wound infection. Arthroscopic acromioplasty (n=32) [1117]: operative stiffness (12.5%) Arthroscopic (closed percutaneous) acromioplasty (n=23) [1118]: pain (39.1%), capsulitis (21.7%), atrophy of the deltoid muscle (8.7%), deep wound infection (4.3%) Open acromioplasty (n=30) [1117]: operative stiffness (10.0%) Open acromioplasty (n=23) [1118]: pain (39.1%). Open rotator cuff repair using non-absorbable braided No. 3 Ethibond (0.7 mm diameter) and a modified Mason Allen technique) (n=50) [1119]: pain (4%), infection (4%). Open rotator cuff repair using 1.0 mm absorbable braided PDS cord and a modified Kessler technique (n=50) [1119]: pain (4%), infection (2%). Open anterior acromioplasty using either Neer's technique or a modified technique not detaching the deltoid origin (n=10 in either group) [1120]: delayed wound healing (5%).
Jacobs et al. [87]	No/limited reporting of complication. The SR itself did not find reporting of complications.
Drazin et al. [86]	Repair of Pars Interarticularis Defect by Segmental Wire Fixation (n=20) [1121]: wire breakage (10%), wire pulled out on one side (5%).

Study	Complications
	Direct repair of spondylolytic defects (n=4) [1122]: unilateral screw breakage (25%), residual complaints of persistent, intermittent low back soreness (25%). Repair of the pars Interarticularis Defect with a cable-screw construct (n=7) [1123]: Prolonged bone graft site pain (14.3%) [1123], fracture of a cable after an altercation with another boy (14.3%). Buck's repair of the spondylolytic lesion (n=10) [1124]: Operative drill breakage (10%). Scott's fusion (n=3) [1125]: non-union (66%) Direct repair with a hook screw [1126] (n=113): pseudoarthroses (13.3%), loosening of nuts (6.2%), wound sloughing (5.3%). Scott wiring technique (n=22) [1127]: urinary retention (9.1%), superficial wound infection (9.1%), wire rupture (9.1%), donor site pain (13.6%)
Manchikanti et al. [88]	Percutaneous disc decompression using coblation technology (n=53) [1128]: increased symptom (3.8%), soreness at needled site (76% within 24 hours and 0% at two week follow up), new numbness and tingling sensation (26% within 24 hours and 15% at two week follow up), increased intensity of pre-procedural back pain (15% within 24 hours, and 4% at two week follow up), new area of back pain (15% within 24 hours and 0% at two week follow up).

SR: Systematic review

Appendix 3 NOS assessment of the included comorbidities of CMP studies – case controlled studies (total 68 studies)

	Selection				Comparability	Exposure		
Study	**Is the case definition adequate**	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**
Aguglia et al. [214]	0	1	0	0	0	0	1	1
Aristeguieta et al. [215]	0	0	0	0	0	0	1	1
Arnold et al. [216]	0	0	1	0	0	0	1	1
Atkinson et al. [175]	0	0	0	1	0	0	1	1
Asmundson et al. [174]	0	0	0	0	0	1	1	1
Ayers et al. [237]	0	1	ncp	ncp	ncp	ncg	ncp	0
Ayoubi et al. [238]	0	1	1	1	0	0	1	0
Bair et al. [183]	0	1	0	1	0	1	1	1
Baruth et al. [239]	0	0	ncg	ncg	ncg	ncg	ncg	ncg
Bazzichi et al.[241]	0	0	1	1	0	0	1	0
Bernatsky et al. [184]	0	0	0	0	0	0	0	0
Bischoff-Ferrari et al. [181]	1	1	ncg	ncg	ncg	ncg	ncg	ncg
Black, Goodwin, & Markides, [185]	0	1	0	1	0	0	1	0
Blackman et al. 2013 [234]	0	1	0	1	2	0	1	0
Blackman et al. 2011 [217]	0	1	0	1	0	0	1	nsg
Braden et al. [186]	0	1	0	0	2	0	1	nsg

	Selection				Comparability	Exposure		
Study	**Is the case definition adequate**	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**
Buist-Bouwman et al. [187]	0	1	0	1	2	0	1	nsg
Cakit et al. [188]	0	1	0	0	0	0	1	1
Carbonell-Baeza et al. [218]	0	0	0	0	0	0	ncg	ncg
Ciapparelli et al. [189]	0	0	0	0	0	0	ncg	ncg
Dominick et al. [231]	0	1	0	1	2	0	1	nsg
Fernandez-de-Las-Penas et al. [190]	0	1	1	1	0	0	1	0
Fitzgerald et al. [219]	1	1	0	0	0	0	ncg	0
Gili et al. [191]	0	0	0	0	2	0	1	0
Gureje et al. [192]	0	1	0	1	0	0	1	nsg
Hägg et al. [193]	0	0	1	1	0	0	1	1
Hoogeboom et al. [220]	1	1	0	0	0	0	ncg	nsg
Ijzelenberg et al. [168]	0	0	0	ncg	0	0	1	nsg
Ismail et al. [242]	0	0	1	1	0	0	1	0
Kane et al. [221]	0	0	0	ncg	ncg	0	ncg	0
Kauppila et al.	1	1	ncg	ncg	0	1	ncg	nsg

	Selection				Comparability	Exposure		
Study	**Is the case definition adequate**	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**
[194]								
Klemenc-Ketiš et al. [222]	0	1	ncg	ncg	0	0	ncg	nsg
Korszun et al. [195]	1	0	ncg	ncg	ncg	1	ncg	0
Kurtze et al. [196]	0	1	ncg	ncg	0	0	ncg	nsg
Lee et al. 2012 [223]	0	0	ncg	ncg	0	0	ncg	0
Lee et al. 2007 [166]	0	1	ncg	ncg	0	0	ncg	nsg
Ligthart et al. [240]	0	1	ncg	ncg	ncg	ncg	ncg	ncg
Linder et al. [197]	1	0	ncg	ncg	0	0	ncg	0
Mäkelä et al. [198]	0	0	ncg	ncg	0	0	ncg	0
Malmgren Olsson et al. [199]	0	0	0	1	0	0	1	0
Mangani et al. [200]	1	0	ncg	ncg	0	0	ncg	0
L. A. McWilliams, Cox, & Enns, 2003 [176]	0	0	1	0	2	0	1	nsg
L. A. McWilliams, Goodwin, & Cox, 2004 [177]	0	0	1	1	2	0	1	nsg
Lachlan A. McWilliams &	0	0	1	0	2	0	1	nsg

	Selection				Comparability	Exposure		
Study	**Is the case definition adequate**	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**
Bailey, 2010 [232]								
L. A. McWilliams & Higgins, 2013 [224]	0	0	ncg	ncg	ncg	0	ncg	0
Nilsdotter et al. [180]	1	1	0	1	0	0	1	0
Polatin et al. [178]	0	0	ncg	ncg	ncg	0	ncg	0
Raab et al. [235]	1	0	0	0	ncg	1	0	0
Rat et al. [236]	1	1	ncp	ncp	ncg	ncg	ncg	ncg
Rehm et al. [225]	0	0	ncg	ncg	ncg	0	ncg	0
Sareen et al. [202]	0	0	0	1	2	0	1	nsg
Schofield et al. [233]	0	0	1	1	0	0	1	nsg
Schur et al. [203]	0	0	1	1	2	0	1	0
Shillam et al. [226]	1	0	ncg	ncg	ncg	0	ncg	nsg
Sipilä et al. [204]	0	0	ncg	ncg	ncg	0	ncg	nsg
Siu et al. [229]	0	0	ncg	ncg	ncg	0	ncg	0
Stupar et al. [179]	0	0	ncg	ncg	ncg	0	ncg	0
Tamber et al. [213]	0	0	0	1	2	0	1	nsg
Tashjian et al. [205]	1	0	0	0	0	0	ncg	0
Tikiz et al. [182]	0	0	0	1	0	0	0	0
Tsang et al. [206]	0	0	0	1	2	0	1	nsg
van Dijk et al. [207]	1	0	0	0	ncg	0	ncg	0

	Selection				Comparability	Exposure		
Study	**Is the case definition adequate**	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**
Verri et al. [208]	0	0	0	0	ncg	0	1	1
Von Korff et al. [167]	0	1	0	1	0	0	1	nsg
Wesseling et al. [230]	1	0	0	ncg	ncg	0	ncg	0
Whitson et al. [209]	1	0	0	0	ncg	0	1	0
Williams Russo et al. [212]	1	1	ncg	ncg	ncg	1	ncg	0
Wolf et al. [211]	1	0	0	ncg	ncg	0	ncg	0

Ncg: no control group
Nsg: no separated into groups

Appendix 4 NOS assessment of the included comorbidities of CMP studies – cohort studies (total 4 studies)

	Selection				Comparability	Outcome		
Study	**Representativeness of the exposed cohort**	**Selection of the non exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design of analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**
Raphael et al. [201]	1	ncg	1	0	ncg	0	1	0
Singh et al. (hip OA) [227]	1	ncg	1	0	ncg	0	1	0
Singh et al. (knee OA) [228]	1	0	1	0	0	0	1	nsg
Wolfe et al. [210]	1	ncg	1	0	ncg	0	1	0

Ncg: no control group
Nsg: no separated into groups

Appendix 5 Mental and behavioural disorders as comorbidity or accompanying symptoms of chronic SP – percentage data within sample - 1

Studies	Major depression/depression	Dysthymic disorder	GAD	All anxiety disorders	Obsessive compulsive disorder	Panic disorder	Alcohol use disorder	Abuse or dependence on other substances
Atkinson et al. [175]	Life time prevalence of major depressive episode: 32% Diagnosed with a major depressive episode:21.6% Episodes of depression during the last six months : Almost all back pain patients have recurrent major depression (exact number not given.) Single episode: 1 (3.2%) Two episodes: 4 (12.9%) Three episodes: 9 (29%) Four episodes: 2 (6.5%) Five or more episodes: 15 (48.4%) Onset of depression before pain: 41.9% onset after age of pain initiation was 58.1%	Prevalence: 23.7%	Lifetime rates: 22.7%. 6 month prevalence: 13.4%	All anxiety disorders pooled together: 21.6%	Lifetime rates: 13.4%	Lifetime rates: 8.2% Prevalence rate: 7.2%	Lifetime prevalence: 64.9% Prevalence rate: 12.4% The proportions developing their illness before and after age of pain onset: before pain onset: 80.9% after pain onset: 19.1% History of onset of alcohol use disorders was not changed by chronic pain.	The use of cannabis: 11.3% The prevalence for other substance abuse or dependence disorders: 4.1%
Hägg et al. [193]	Major depression (diagnosed with Zung Depression Scale): 9%	No data						
Polatin et al. [178]	Life time major depression (as assessed with Structured clinical interview for DSM-III-R): 64%	Life time dysthymia: 2%	Life time GAD: 2%	Life time Anxiety disorders: 19%	Obsessive compulsive disorders: 2%	Panic disorders: 3%	No data	Substance abuse:36% psychoactive substance use disorders: 36%
Verri et al.	Major depression disorder (single	Dysthymia:	GAD: 23	No data	Obsessive	Panic	No data	

Studies	Major depression/depression	Dysthymic disorder	GAD	All anxiety disorders	Obsessive compulsive disorder	Panic disorder	Alcohol use disorder	Abuse or dependence on other substances
[208]	episode in progress): 2 (5.7%) Major depression disorder (in full remission): 4 (11.4%) Recurrent major depression disorder: 1 (2.8%)	7 (20%)	(65.7%)		compulsive disorder: 0	disorder: 1 (2.8%)		
Von Korff et al. [167]	Compared with general public without chronic SP:							
	Major depression: 12.6% (SE:0.7)	Dysthymia: 5.6% (SE:0.6)	GAD: 6.4% (SE:0.7)	Any anxiety: 26.5% (SE:1.2)	No data	Panic disorder: 4.8% (SE:0.5)	Alcohol abuse or dependence: 4.0% (SE:0.6) Alcohol dependence: 2.1% (SE:0.4)	Any substance: 4.8% (SE:0.8) Mental disorders not associated with chronic SP are: *drug abuse or dependence, drug dependence.*
Whitson et al. [209]	For vertebral fracture group, there are 211 participants and the percentage of accompanying symptoms and comorbidities are as following: Symptoms in previous month: feeling sad, depressed, or blue: 33.2% depression or anxiety: 21.8%	No data		Symptoms in previous month: anxiety, worry, or tension: 45.7% depression or anxiety: 21.8%	No data			
Schofield et al. [233]	Depression/mood affective disorders: 5.4%	No data						
Linder et	Depression episode: 26.1%	No data						

Studies	Major depression/depression	Dysthymic disorder	GAD	All anxiety disorders	Obsessive compulsive disorder	Panic disorder	Alcohol use disorder	Abuse or dependence on other substances
al. [197]	Recurrent depression: 24.4%							

GAD: Generalized anxiety disorder
SE: Standard error

Appendix 6 Mental and behavioural disorders as comorbidity or accompanying symptoms of chronic SP – percentage data within sample - 2

Studies	Mood disorder	Phobia	Somatoform disorder	Bipolar	PTSD	Other
Atkinson et al. [175]	No data					At least one psychiatric disorder (other than tobacco use disorder): 81.4% A psychiatric disorder occurred recently in pain patients: (41.2%)
Polatin et al. [178]	No data	Phobic disorders: (11%)	Somatoform pain disorder: (97%) Somatization: (1%) Hypochondriasis: (1%)	Bipolar: (2%)	PTSD: (1%)	Psychotic disorders: (3%), others Axis I disorders: (3%) The percentage of each Axis II disorder is listed as the following: Paranoid PD: (33%) Schizoid PD: (4%) Schizotypal PD: (4%) Passive-aggressive PD: (12%) Self-defeating PD: (10%) Dependent PD: (3%) Obsessive compulsive PD: (6%) Avoidant PD: (14%) Histrionic PD: (4%) Narcissistic PD: (5%) Antisocial PD: (5%) Borderline PD: (15%) Not otherwise specified PD: (2%)
Schofield et al. [233]	No data					Mental/behavioural disorders: 10.2%
Verri et al.	No data	Simple phobia: 9	Somatoform	No data		Other classes of diagnosis: 2

Studies	Mood disorder	Phobia	Somatoform disorder	Bipolar	PTSD	Other
[208]		(25.7%) Social phobia: 0	disorders: 12 (34.3%)			(5.7%) No axis I disorders: 6 (17.1%)
Von Korff et al. [167]	Any mood: 17.5% (SE:1.1)	Social phobia: 8.3% (SE:0.8) Specific phobia: 12.5% (SE:1.0) Mental disorders not associated with chronic SP are: *agoraphobia without panic*	No data	Bipolar I or II: 4.4% (SE:0.6)	PTSD: 7.3% (SE:0.7)	All mental disorders: 35.0% (SE:1.7)

PTSD: Post traumatic stress disorder
PD: Psychotic disorder
SE: Standard error
SP: Spinal pain

Appendix 7 Mental and behavioural disorders as comorbidity or accompanying symptoms of chronic SP – OR - 1

Studies	Major depression/depression	Dysthymic disorder	GAD	All anxiety disorders	Panic disorder	Alcohol use disorder	Abuse or dependence on other substances
Buist-Bouwman et al. [187]	Compared with general public without chronic SP:						
	No data			Anxiety disorder: 1.6 (1.3-2.0)	No data		Substance use: 1.3 (0.9-1.8).
Gureje et al. [192]	Compared with general public without chronic SP:						
	No data			Any anxiety disorder: 1.5 (0.9-2.5)	No data		Any substance disorder: 3.2 (1.2-8.0)
Hägg et al. [193]	Compared with general public without back pain: Major depression: 6.2 (1.9–20.6)	No data					
McWilliam et al. 2004 [177]	Compared with general public without chronic SP:						
	Depression: 1.87 (1.49-2.36)	No data	GAD: 2.54 (1.67-3.85)	No data	Panic attacks: 2.69 (2.00-3.62)	No data	
Tsang et al. [206]	Compared to international general public without chronic SP:						
	Depression-anxiety disorder: 2.0 (1.8-2.1).	No data		Depression-anxiety disorder: 2.0 (1.8-2.1).	No data		
Von Korff et al. [167]	Compared with general public without chronic SP:						
	Major depression: 2.5 (2.0-3.1)	Dysthymia: 3.2 (2.3-4.5)	GAD: 2.6 (2.0-3.5)	Any anxiety: 2.3 (1.9-2.7)	Panic disorder: 2.0 (1.5-2.6)	Alcohol abuse or dependence: 1.6 (1.2-2.2)	Any substance: 1.6 (1.2-2.2) Mental

Studies	Major depression/depression	Dysthymic disorder	GAD	All anxiety disorders	Panic disorder	Alcohol use disorder	Abuse or dependence on other substances
						Alcohol dependence: 2.0 (1.4-2.9)	disorders not associated with chronic SP are: *drug abuse or dependence, drug dependence.*

GAD: Generalized anxiety disorder
SP: Spinal pain

Appendix 8 Mental and behavioural disorders as comorbidity or accompanying symptoms of chronic SP – OR - 2

Studies	Suicidal ideation, suicide plan, and suicide attempt	Mood disorder	Phobia	Bipolar	PTSD	Other
Braden et al. [186]	Compared with general public without chronic SP:					
	Suicidal ideation: 1.4 (1.2-1.6)(P<0.001) Suicide plan: 1.5 (1.1-1.9)(P<0.01) Suicide attempt: 1.6 (1.3-2.1)(P<0.001)	No data				
Buist-Bouwman et al. [187]	Compared with general public without chronic SP:					
	No data	Mood disorder: 1.7 (1.3-2.2)	No data			
Gureje et al. [192]	Compared with general public without chronic SP:					
	No data	Any mood disorder: 2.2 (1.2-4.0) Any mental disorders: 1.7 (1.2-2.5)	No data			
Von Korff et al. [167]	Compared with general public without chronic SP:					
	No data	Any mood: 2.5 (1.9-3.2)	Social phobia: 1.7 (1.3-2.2) Specific phobia: 2.1 (1.7-2.6) Mental disorders not associated with chronic SP are: *agoraphobia without panic*	Bipolar I or II: 2.0 (1.4-2.9)	PTSD: 2.6 (2.1-3.3)	All mental disorders: 2.3 (1.8-2.9)

Studies	Suicidal ideation, suicide plan, and suicide attempt	Mood disorder	Phobia	Bipolar	PTSD	Other
Lachlan A. McWilliams & Bailey et al. [232]	No data					Compared with general public without chronic SP: Attachment style ratings (OR adjusted for gender, marital status, education level, race, age, and the other attachment style ratings): Secure: 0.91 (0.84–0.98) Avoidant: 1.16 (1.08–1.25) Anxious: 1.08 (0.98–1.19)

Comorbidities/accompanying symptoms of no association were italicised
PTSD: Post traumatic stress disorder
SP: Spinal pain

Appendix 9 Mental and behavioural disorders/symptoms as comorbidity/accompanying symptoms of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Lee et al. [166]	Beijing participants (percentage and SE): Mood disorder: Major depressive disorder with hierarchy: 3.9% (SE: 1.8) Dysthymia: 1.1% (SE: 0.5) Any mood: 3.9% (SE: 1.8) Anxiety disorders: GAD: 2.3% (SE: 0.5) Panic disorder: 0.4% (SE: 0.4) Agoraphobia without panic: 0 PTSD: 0 Social phobia: 0 Specific phobia: 3.5% (SE: 2.3) Any anxiety: 5.3% (SE: 2.3) Substance disorder: Alcohol abuse or dependence: 4.3% (SE: 0.9) Alcohol dependence: 1.7% (SE: 1.5) Drug abuse or dependence: 0.2% (SE: 0.0) Drug dependence: 0 Any substance: 4.5% (SE: 0.9) Any mental disorder: 10.5% (SE: 3.1)	Compared with general public without arthritis: Beijing: Dysthymia: 4.0 (1.1-14.4) GAD: 2.4 (1.3-4.5). Non-significant: *Major depression disorder with hierarchy: 1.8 (0.5-6.6)* *Any mood disorder: 1.7 (0.5-6.2)* *Panic disorder: 1.0 (0.1-10.1)* *Specific phobia: 2.3 (0.5-10.5)* *Any anxiety: 1.8 (0.7-4.5)* *Alcohol abuse or dependence: 1.9 (0.9-4.1)* *Alcohol dependence: 2.4 (0.4-15.9)* *Drug abuse or dependence: 2.6 (0.2-42.7)* *Any substance: 1.9 (0.9-4.0)* *All mental disorders: 1.6 (0.8-3.1)*
	Shanghai participants: Mood disorder: Major depression disorder with hierarchy: 5.7% (SE: 3.6) Dysthymia: 0.3% (SE: 0.3) Any mood: 5.7% (SE: 3.6) Anxiety disorders: GAD: 3.6% (SE: 3.5) Panic disorder: 0 Agoraphobia without panic: 0 PTSD: 0.8% (SE: 0.6) Social phobia: 0 Specific phobia: 7.5% (SE: 4.2) Any anxiety: 7.9% (SE: 4.2) Substance disorder: Alcohol abuse or dependence: 0.5% (SE: 0.4) Alcohol dependence: 0.5% (SE: 0.4) Drug abuse or dependence: 0 Drug dependence: 0 Any substance: 0.5% (SE: 0.4) Any mental disorder: 10.0% (SE: 4.3)	Shanghai: Major depression disorder with hierarchy: 8.0 (1.7-38.4) Any mood disorder: 5.7 (1.3-26.1) GAD: 15.4 (2.9-83.3) Specific phobia: 6.9 (1.3-37.0) Any anxiety: 5.9 (1.3-25.9) Any mental disorder: 3.7 (1.2-11.4) Non-significance: *Dysthymia: 0.8 (0.1-8.0)* *Alcohol abuse or dependence: 1.0 (0.2-5.6)* *Alcohol dependence: 1.9 (0.3-13.2)* *Any substance disorder: 1.0 (0.2-5.4)*

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Van Dijk et al. [207]	Psychiatric diseases: 26.3%	
Wolfe et al. [210]	The cross-sectional prevalence of self-reported depression: 15.2% (95% CI 14.7-15.7%). The annualized incidence (new case after entry to study) rate for self-reported depression: 5.5 (95% CI 5.3-5.7) per 100 patient years. The estimated cumulative risk of self-reported depression at 9 years follow up: 38.3% (95% CI 36.6-40.1%)	No data
Black et al. [185]		Compared with general public without arthritis: Depressive symptoms:1.87 (1.58-2.22)
Braden et al. [186]		Compared with general public without arthritis: After adjusted for sociodemographic factor (age, gender, race/ancestry, marital status, education status, religion, log-transformed income: Suicidal ideation: 1.7 (1.4-2.1) Suicidal plan: 2.0 (1.5-2.6) *Suicide attempt: 1.4 (95% CI 1.0-1.8)* But if they were adjusted further with lifetime mood or anxiety disorder, lifetime alcohol or drug abuse/dependence, then OR did not show significant difference.
Sareen et al. [202]	No data	Compared with general public without arthritis: After adjusting for age, gender, low income, education, past-year mental disorders (major depression, dysthymia, bipolar disorder, alcohol use disorder and substance use disorder):

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
		Any past-year anxiety disorder: 2.28 (1.58-3.29). After adjusted for any bone or joint condition versus without bone or joint condition: PTSD: 2.52 (1.67-3.81), Panic attacks: 2.00 (1.22-3.28). But there is no significant difference for *agoraphobia without panic [2.23 (0.97–5.11)], GAD [1.13 (0.60–2.13)], social phobia [0.96 (0.66–1.39)], and simple phobia [1.22 (0.78–1.93)* for any bone or joint condition versus without bone or joint condition.
Tsang et al. [206]		Compared to international general public without arthritis: Depression-anxiety disorder: 1.6 (1.4-1.7)
McWilliams et al. 2004 [177]		Compared with general public without arthritis: Depression: 1.48 (1.16-1.88) Panic attacks: 2.09 (1.54-2.83) GAD: 2.17 (1.42-3.33)
McWilliams et al. 2003 [176]		Compared with general public without arthritis: Any mood disorder: 2.78 (2.06-3.75) Depression: 2.82 (2.05-3.89) Dysthymia: 2.07 (1.26-3.42) Any anxiety disorder: 2.86 (2.06-3.97) GAD: 2.30 (1.45-3.67) Panic disorder with or without agoraphobia: 4.27 (2.39-7.61) Simple phobia: 2.20 (1.43-3.38) Social phobia: 1.92 (1.31-2.82) Agoraphobia with or without panic: 3.19 (1.87-5.46) Post-traumatic stress disorder: 3.69 (2.40-5.68)

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Buist-Bouwman et al. [187]	Mental disorder: 28.1%	Compared with general public without rheumatism: Anxiety disorder is 1.4 (1.1-1.8) Mood disorder is 1.5 (1.1-2.0) Substance use is 1.8 (1.3-2.6)
Williams Russo et al. [212]	Psychiatric disease and/or Geriatric Depression Scale (GDS) > 11: 4 (7.84%) (for these four patients, one was for mania-depression and on medication, one was for depression and on medication, the other two were for probable depression as GDS>11).	
Blackman et al. 2011 [217]	For arthritis/other joint problems, 25.9% (95% CI 20.0-32.0) of them have long-term emotional, developmental or behavioural problem, and 22.1% (95% CI 16.2-29.3) of them have ADD/ADHD. Of the arthritic/other joint problems children, 26.0% (95% CI 19.8-33.4) have difficulties in learning, understanding or paying attention, 12.5% (95% CI 8.5-18.0) of them have difficulties in speaking, communicating or being understood, 33.4% (95% CI 26.5-41.3) of them have difficulty with feeling anxious or depressed, 27.1% (95% CI 20.6-34.8) of them have difficulty with behaviour problems, such as acting out, fighting, bullying or arguing.	
Fitzgerald et al. [219]	The prevalence listed below are the combined results of both groups ("standard exercise" group and "agility and perturbation" group): Depression: 32 (17.5%) Memory problems: 15 (8.2%)	
Hoogeboom et al. [220]	For knee and/or hip OA (n=401): Depressed (Hospital Anxiety and Depression Scale ≥ 8): 99 (24%)	No data
Klemenc-Ketiš et al. [222]	Depression: 23 (20.6%) Anxiety: 25 (22.3%)	Compared to GP-visiting general public without osteoarthritis and rheumatic diseases:

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
		The OR for osteoarthritis/rheumatic diseases patients to have depression based on Zung depression score≥50 was *1.23 (95% CI 0.62-2.41)* and to have anxiety based on Zung anxiety score ≥50 was 2.59 (95% CI 1.29-5.20).
L. A. McWilliams & Higgins et al. [224]	Borderline personality disorder symptoms during the past year: 1553 (27.3%)	
Singh et al. (knee OA) [228]	Primary total knee arthroplasty: Two year follow up: Anxiety: 6% Depression: 11% Five year follow up: Anxiety: 5% Depression: 8% Revision total knee arthroplasty: Two year follow up: Anxiety: 5% Depression: 8% Five year follow up: Anxiety: 3% Depression: 6%	No data
Lachlan A. McWilliams & Bailey et al. [232]	No data	Compared with general public without arthritis: Attachment style ratings (OR adjusted for gender, marital status, education level, race, age, and the other attachment style ratings): *Secure: 0.94 (0.85–1.03)* Avoidant: 1.15 (1.04–1.28) *Anxious: 1.07 (0.93–1.23)*
Blackman et al. 2013 [234]	Of the chronic bone, joint, muscle problem children, their prevalence (SE) for the following conditions were: ADHD: 29% (3.4) Depression: 20.9% (3.4) Anxiety: 20.3% (2.9) Learning disability: 38% (3.3) Behaviour problem at least 12 months:	Compared with general public without arthritis (participants were all children): Of the chronic bone, joint, muscle problem children, their ORs for the following conditions were:

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
	27.1% (2.5) Of the chronic bone, joint, muscle problem children, their prevalence (SE) for the following emotional and behavioural problems: Emotional functioning: Feels worthless or inferior:10.8% (2.9) Is unhappy, sad, or depressed: 10.8% (2.9)	ADHD: 3.3 (2.2-4.9) Depression: 5.1 (3.2-8.2) Anxiety: 4.1 (2.7-6.1) Learning disability: 4.7 (3.3-6.5) Behaviour problem at least 12 months: 4.2 (3.2-5.6)
Raab et al. [235]	Psychiatric disorders: 32 (9.3%) Depression: 17 (4.9%) Anxiety disorder: 7 (2%)	
Nilsdotter et al. 2003 [180]	Psychiatric disease: 2.6%	No data

Comorbidities/accompanying symptoms of no association were italicised
ADHD: Attention deficit hyperactive disorder
CI: Confidence interval
GAD: Generalized anxiety disorder
GP: General practitioner
OA: Osteoarthritis
OR: Odds ratio
PTSD: Post traumatic stress disorder
SE: Standard error

Appendix 10 Diseases/symptoms of the genitourinary system as comorbidity or accompanying symptoms of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Whitson et al. [209]	Incontinence: 35.6%	
Schofield et al. [233]	Genitourinary system diseases: 2%	No data
Hägg et al. [193]	No data	Compared with general public without back pain Back pain during pregnancy: 2.3 (1.1-4.5) Back pain during menstruation: 2.7 (1.5-5.1), Increased number of deliveries: 1.6 (1.1-2.1)

CI: Confidence interval

Appendix 11 Other comorbidities/accompanying symptoms or findings of chronic SP

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Hägg et al. [193]	Smoking: 42% general morbidity: 35%	Compared with general public without back pain: Smoking: 2.3 (1.6 - 3.6) General morbidity: 3.6 (2.2 - 5.9) Compared with general public with non-chronic back pain: *Smoking:1.6 (1.0 - 2.6)* *General morbidity: 1.0 (0.6 – 2.2)*
Von Korff et al. [167]	HIV: 0.3% (SE:0.1) Cancer: 0.8% (SE:0.4) Any physical disease: 55.3% (SE:1.8) All mental, pain or physical disorder: 87.1% (SE:1.1)	Compared with general public without chronic SP: HIV: 5.0 (1.9-13.0) Any physical disease: 2.0 (1.7-2.4) All mental, pain or physical disorder: 4.4 (3.5-5.6) *Cancer: 0.8 (0.3-2.1)*
Whitson et al. [209]	Dizziness or lightheaded: 20.9% Cancer: 26.1% Amputation: 0.5%	
Schofield et al. [233]	Injury/accident: 14.0% Neoplasms (tumours/cancers): 0.3% Other: 7.8%	No data

Comorbidities/accompanying symptoms of no association were italicised
CI: Confidence interval
SE: Standard error

Appendix 12 Diseases/symptoms of the genitourinary system as comorbidity or accompanying symptoms of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Van Dijk et al. [207]	Urogenital disease: 44.4% Renal disease: 11.2%	
Mangani et al. [200]	Of the entire group, the prevalence of comorbidities are as following: Renal disease: 2.8%	
Fitzgerald et al. [219]	The prevalence listed below are the combined results of both groups ("standard exercise" group and "agility and perturbation" group): Kidney disease: 2 (1.1%)	
Hoogeboom et al. [220]	For hip and/or knee OA (n=401): Kidney/liver disease: 4 (1%)	
Singh et al. (hip OA) [227]	Primary total hip arthroplasty: Two year follow up: Renal disease: 5% Five year follow up: Renal disease: 4% Revision total hip arthroplasty: Two year follow up: Renal disease: 4% Five year follow up: Renal disease: 3%	
Singh et al. (knee OA) [228]	Primary total knee arthroplasty: Two year follow up: Renal disease: 6% Five year follow up: Renal disease: 4% Revision total knee arthroplasty: Two year follow up: Renal disease: 4% Five year follow up: Renal disease: 2%	
Wesseling et al. [230]	For self-reported comorbidity of >1% prevalence: Chronic urolithiasis: 16 (1.6%) Prolapsed uterus: 42 (4.2%)	
Raab et al. [235]	Diseases of the kidneys or the urinary tract: 16 (4.7%) Renal insufficiency: 1 (0.3%) Kidney stone: 4 (1.2%) Gynaecological diseases: 12 (5%)	
Ayers et al. [237]	Renal disease: 3.1%	No data

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Nilsdotter et al. 2003 [180]	Kidney disease: 0%	

CI: Confidence interval
OR: Odds ratio

Appendix 13 Ear, nose, throat, and eye disorders comorbidity of arthritis

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI
Van Dijk et al. [207]	Eye, ear, nose, throat and larynx disease: 96.1%	
McWilliam et al. 2003 [176]	Blindness, deafness, or severe visual or hearing impairment: 9.9%	No data

CI: Confidence interval
OR: Odds ratio

Appendix 14 Circulatory diseases/symptoms as comorbidity/accompanying symptoms of fibromyalgia

Studies	Percentage of comorbidity/accompanying symptoms	OR and 95% CI or other findings
Bernatsky et al. [184]	The comorbidities of the 180 participants are as following: Hypertension/vascular: 18 (10%)	
Shillam et al. [226]	Cold hands: 113 (66%) Bruising easily: 113 (66%)	No data

CI: Confidence interval
OR: Odds ratio

Appendix 15 Other findings of fibromyalgia

Studies	Other findings
Carbonell-Baeza et al. [218]	The results of the Fibromyalgia Impact Questionnaire were reported in the order of median, 25th percentile, 75th percentile: Pain (n=108): 7.2, 6, 8.5 Fatigue (n=109): 8.8, 7.5, 9.55 Rested (n=109): 9.2, 8, 9.6 Stiffness (n=109): 8.1, 6.35, 9.4 Anxiety (n=109): 6.9, 5.2, 9 Depression (n=109): 6.5, 4.55, 8.35

Shillam et al. [226]	Others: Sensitivity to light or sound: 128 (75%) Profuse sweating or feeling hot: 125 (73%) Skin tenderness: 134 (78%) Accident prone: 97 (57%) Swelling: 104 (61%) Inability to enjoy life: 101 (59%) Pelvic pain: 59 (35%)

Appendix 16 Chinese medicine pain questionnaire

Code: | | | | | | | | | **Date:** | | | | | | | | |

Chinese Medicine Pain Questionnaire

Part A. To be completed by patients

Please choose as many words or phrases you need to best describe your pain and / or accompanying symptoms.

Where is your pain?

Head , Neck & Shoulder	Upper limbs	Lower limbs	Front of the body trunk	Back of the body trunk
Frontal head	Upper arm	Hip	Chest	Between shoulder blades
Sides of the head	Elbow	Thigh	Stomach	Middle Back
Back of the head	Forearm	Knee	Abdomen	Lower back
Vertex	Wrist	Front of the leg	Groin	Sacrum
Neck	Hand	Calf	Side of the body	Buttocks
Shoulder	Fingers	Ankle		
Shoulder blades		Heel		
		Sole		
		Toes		

What is the quality of your pain?

Cold	Pulling	Distending	Fixed location	Moving from one spot to another	Sharp
Pricking	Numbness	Dull	Dull pain with weakness	Hot	Burning
Not known	Other (please specify)				

What is your pain rhythm?

Code: | | | | | | | | | **Date:** | | | | | | | | |

During the course of the day, when do you have pain?

All the time	Recurrent	Fluctuate	Worse during the day, better at night	Worse at night, better during the day
Worse when first get up	Worse at the end of the day	Worse in the morning	Worse at lunch time	Worse in the afternoon
Not known	Other (please specify)			

What worsens your pain?

Environmental changes	Cold weather	Wet weather	Windy days	Weather change	Hot weather
Exercises or sporting	Standing	Walking	Lying-down	Physical work	Sitting
	Lifting	Bending	Any movement	Going up/down stairs	Driving
Physiological & psychic changes	After eating	Being hungry	Bad night sleep	Stress	Being emotional
Others	Pressure on the area	Sex	Everything	Household chores	
Not known					
Other (please specify)					

For female patients

Before period	During period	After period

Code: | | | | | | | | | Date: | | | | | | | | |

What relieves your pain?

Environmental changes	Cold weather	Wet weather	Windy days	Hot packs	Cold packs
	Hot weather	Warm/hot bath	Warm/hot shower		
Exercises or sporting	Standing	Walking	Lying-down	Sitting	
	Gentle massage	Gentle exercise	Any movement	Resting	Driving
Physiological & psychic changes	Eating	Being hungry	Deep breathing	Belching	Bowel movement
	Pain killer	Pressure on the pain area	Keeping my mind off pain	Being with other people	Alcohol
	Reading	Sleep	Working	Watching TV	
Others	Keeping busy	Sex	Everything	Household chores	Nothing
Not known					
Other (please specify)					

For female patients

Before period	During period	After period

Code: | | | | | | | | | **Date:** | | | | | | | | |

Do you have any other symptoms?

Swollen joints	Red and hot joints	Cold joints	Limited movement	Distention sensation in the abdomen	Indigestion
Heavy sensation in the body	Cold hands and feet	Cold lower back or knees	Feeling cold easily	Feeling hot easily	Insomnia
Night sweating	Irritable	Dry or sore throat	Flushed face	Hot palms	Thirsty
Watery Diarrhea	Mushy stools	Dry stools	Constipation	Dry skin	Leak when sneezing or cough
Frequent urination at night	Frequent urination	Poor concentration	Poor memory	Low libido	Poor appetite
Feeling tired easily	Sigh often	Need deep breath	Short of breath	Sweat upon mild activities	Catch cold easily
Abdominal Distention	Stuffiness in the chest	Feeling nervous easily	Feeling depressed	Reflux	Belching
Nausea	Dizziness	Skin itch			
Others (please specify)					
For female patients	Abdominal pain during or before period periods	Low back pain during or before periods	Dark blood	Light blood (pink)	Bleeding with clots
	Excessive bleeding	Light bleeding	Delayed periods	Early periods	Irregular periods
	Excessive watery discharge	Yellow discharge			
	Other (please specify)				

Appendix 17 Beck Depression Inventory

Code: | | | | | | | | | **Date:** | | | | | | | | |

BDI-II

Date:

Name: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today.** Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item18 (Changes in Appetite).

1. Sadness
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I fell more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-criticalness
- 0 I don't criticize or blame my self more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal thoughts or wishes
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying
- 0 I don't cry anymore than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

_____ Subtotal Page1 **Continue on Back**

Code: | | | | | | | | | Date: | | | | | | | | |

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do ever much.
3 I don't have enough energy to do anything.

16. Changes in sleeping pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite all.
3b I crave food all the time.

19. Concentration difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of interest in sex.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

_____ Subtotal Page 2
_____ Subtotal Page 1
_____ Total Score

SF-36 HEALTH SURVEY

INSTRUCTIONS: This questionnaire asks for your views about your health, how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent 1

Very good 2

Good 3

Fair 4

Poor 5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago 1

Somewhat better now than one year ago 2

About the same as one year ago 3

Somewhat worse now than one year ago 4

Much worse now than one year ago 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking **more than one kilometre**	1	2	3
h. Walking **half a kilometre**	1	2	3
i. Walking **100 metres**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

No bodily pain 1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all 1

A little bit.....2

Moderately 3

Quite a bit 4

Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt down?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Appendix 19 Roland Morris Disability Questionnaire

Code: | | | | | | | | | **Date:** | | | | | | | | |

Roland-Morris Disability Questionnaire

Australian English version.

When you have pain, you may find it difficult to do some of the things you normally do.

This list contains some sentences that people have used to describe themselves when they have pain. When you read them, you may find that some stand out because they describe your situation *today*. As you read the list, think of yourself ***today***. When you read a sentence that describes your situation ***today***, put a tick (√) against it. If the sentence does not describe your situation, then leave the space blank and go on to the next one. **Remember, only tick the sentence if you are sure that it describes your situation *today*.**

1. I stay at home most of the day because of the pain.
2. I change position frequently to try and get comfortable.
3. I walk more slowly than usual because of the pain.
4. Because of the pain, I am not doing any of the jobs that I usually do around the house.
5. Because of the pain, I use a handrail to climb stairs.
6. Because of the pain, I lie down to rest more often than usual.
7. Because of the pain, I have to hold on to something to get out of a lounge chair.
8. Because of the pain, I ask other people to do things for me.
9. I get dressed more slowly than usual because of the pain.
10. I only stand up for short periods of time because of the pain.

Code: | | | | | | | | | **Date:** | | | | | | | | |

11. Because of the pain, I try not to bend or kneel down.

12. I find it difficult to get out of a dining chair because of the pain.

13. The pain is there most of the time.

14. I find it difficult to turn over in bed because of the pain.

15. I do not feel like eating much because of the pain.

16. I have trouble putting on my socks (or stockings) because of the pain.

17. I only walk short distances because of the pain.

18. I sleep less than usual because of the pain.

19. Because of the pain, I get dressed with help from someone else.

20. I sit down for most of the day because of the pain.

21. I avoid heavy jobs in the house because of the pain.

22. Because of the pain,, I am more irritable and bad tempered with people than usual.

23. Because of the pain,, I climb stairs more slowly than usual.

24. I stay in bed most of the time because of the pain.

Note
This questionnaire is a modified version of MAPI 2005, which was taken from Roland MO, Morris RW. A study of the natural history of back pain. Part 1: Development of a reliable and sensitive measure of disability in low back pain. Spine 1983; 8: 141-144.

Appendix 20 Pain and medication diary

Code: | | | | | | | | | **Date:** | | | | | | | | |

Pain and Medication Diary

Short trial title: EA and OM reduction

Office use only										
Pre-treatment:	Week	1	2	3	4					
During treatment:	Week	5	6	7	8	9	10	11	12	13
		14								
Post treatment:	Week	18	22	26						
Period: From	/	/	**to**	/	/					

Please complete the following forms each week

Form 1	Pain - Daily
Form 2	Pain medications Taken – Daily
Form 3	Side Effects of Pain Medications – Weekly
Form 4	Report of Adverse Event for acupuncture (if applicable) – Weekly

We hope and expect

you will be able to reduce your

opioid medications during the study

1

Code: | | | | | | | | | Date: | | | | | | | | |

Explanation on how to use the Subject Diary (Treatment period)

Welcome to the study. Please complete this diary, as it is a very important part of the assessment.

Your Diary gives us information about

- the dosage of pain medications you are taking
- the severity of related side effects
- the amount of pain you are experiencing and
- aspects of your life which may be affected by the pain

Please take 5 minutes each day to fill in the diary, and **do so at the end of the day.** Please also remember to complete forms 3 and 4 at the end of the week.

Please only rate the intensity and unpleasantness of the pain for which you are referred to Pain Services at the Royal Melbourne Health or the Caulfield Pain Management and Research Centre at the Caulfield Hospital.

When you finish a one-week assessment, please check whether you have answered all the questions. Bring the completed diary with you when you come for treatment.

Alternatively, please return the completed four one-week assessments you have done in the last month by post to

Dr Zhen Zheng
Discipline of Chinese Medicine
PO BOX 71
RMIT University
Bundoora, Vic 3083

The data collected may be published as group data, and no personal information will be identified.

Thanks for your co-operation.

Patient Initial: | | | | | | | **Patient No.:** | | | | **Date:** | | | | | | | |

The following are examples of how to use the scales enclosed and how to record the pain medication doses on Form 2.

- For example, if you draw a line on the scale, the distance from 0 to the line is 6.0 cm, which means your pain is 6 out of 10.

How intense is your pain **at this moment?**

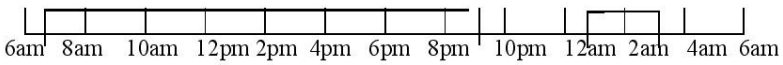
No pain at all — Worst pain imaginable

- For example, if you circle 15 on the left column, this indicates that your pain is strong. If you circle 10 on the right column, this indicates that your pain is "very unpleasant".

How **strong** is the average level of your pain today?		How **unpleasant** is the average level of your pain today?	
20		20	
19		19	
18	EXTREME INTENSE	18	
17	VERY INTENSE	17	VERY INTOLERABLE
16	INTENSE	16	INTOLERABLE
15	STRONG	15	
14		14	VERY DISTRESSING
13	SLIGHTLY INTENSE	13	SLIGHTLY INTOLERABLE
12	BARELY STRONG	12	VERY ANNOYING
11	MODERATE	11	DISTRESSING
10		10	VERY UNPLEASANT
9		9	SLIGHTLY DISTRESSING
8	MILD	8	ANNOYING
7		7	UNPLEASANT
6	VERY MILD	6	SLIGHTLY ANNOYING
5	WEAK	5	SLIGHTLY UNPLEASANT
4	VERY WEAK	4	
3		3	
2		2	
1	FAINT	1	
	NO PAIN SENSATON	0	NEUTRAL

- If you draw a line from 6: 50 am to 9:10 pm it means your pain never stops during this period time. You may use more than one line over the 24 hours if you pain starts then stops, then starts again as shown in the diagram.

When did you feel the pain today?



3

Patient Initial: | | | | | | | **Patient No.:** | | | **Date:** | | | | | | | |

- Pain Medication Taken

Please put the number associated with the pain medications in the related columns (see the listed of pain medications below).

The following example means you took 15 mg of MS Contin, 5 mg of Tramal, 1000mg of Aspirin and 200mg of Celebrex on the day.

Date	**Medication 6**	**Medication 16**	**Medication 17**	**Medication 18**	**Medication**
Time	Doses Taken	Doses Taken	Doses Taken	Doses Taken	Doses Taken
1-2 am					
3-4 am					
5-6 am				**100 mg**	
7-8 am	**5 mg**	**5 mg**	**500 mg**		
9-10 am					
11am-12 pm					
1-2 pm			**500 mg**		
3-4 pm					
5-6 pm				**100 mg**	
7-8 pm	**10 mg**				
9-10 pm					
11am-12 pm					
Total	**15 mg**	**5 mg**	**1000 mg**	**200 mg**	

List of Pain Medications:

1. Anamorph	2. Dilaudid	3. Durogesic	4. Endone
5. Kapanol	6. MS Contin	7. MS Mono	8. Ordine
9. OxyContin	10. OxyNorm	11. Panadeine	12. Panadeine Forte
13.Pethidine Hydrochloride	14. Physeptone	15. Proladone	16. Tramal
17. Aspirin	18. Celebrex	19. other 1	20. Other 2
21. Other 3	22. Other 4		

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Form 1 Day One

1) How intense is your pain **at this moment?**

No pain at all — Worst pain imaginable

2) What is the **highest** level of your pain today?

No pain at all — Worst pain imaginable

3) What is the **average** level of your pain today?

No pain at all — Worst pain imaginable

4) How **strong** is the average level of your pain today?

20	
19	
18	EXTREME INTENSE
17	VERY INTENSE
16	INTENSE
15	STRONG
14	
13	SLIGHTLY INTENSE
12	BARELY STRONG
11	MODERATE
10	
9	
8	MILD
7	
6	VERY MILD
5	WEAK
4	VERY WEAK
3	
2	
1	FAINT
	NO PAIN SENSATON

5) How **unpleasant** is the average level of your pain today?

20	
19	
18	
17	VERY INTOLERABLE
16	INTOLERABLE
15	
14	VERY DISTRESSING
13	SLIGHTLY INTOLERABLE
12	VERY ANNOYING
11	DISTRESSING
10	VERY UNPLEASANT
9	SLIGHTLY DISTRESSING
8	ANNOYING
7	UNPLEASANT
6	SLIGHTLY ANNOYING
5	SLIGHTLY UNPLEASANT
4	
3	
2	
1	
0	NEUTRAL

6) When did you feel the pain today?

6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am 2am 4am 6am

5

Code: ☐☐☐☐☐☐☐☐ Date: ☐☐☐☐☐☐☐☐

Pain Medication Taken

Form 2

7) Please put the number associated with the pain medications in the related columns (see the listed pain medications below).

Date	Medication	Medication	Medication	Medication	Medication
Time	Doses Taken	Doses Taken	Doses Taken	Doses Taken	Doses Taken
1-2 am					
3-4 am					
5-6 am					
7-8 am					
9-10 am					
11am-12 pm					
1-2 pm					
3-4 pm					
5-6 pm					
7-8 pm					
9-10 pm					
11pm-12 am					
Total					

List of Pain Medications:

1. Anamorph	2. Dilaudid	3. Durogesic	4. Endone
5. Kapanol	6. MS Contin	7. MS Mono	8. Ordine
9. OxyContin	10. OxyNorm	11. Panadeine	12. Panadeine Forte
13.Pethidine Hydrochloride	14. Physeptone	15. Proladone	16. Tramal
17. Aspirin	18. Celebrex	19. other 1	20. Other 2
21. Other 3	22. Other 4		

8) Did you have any of the consultations (see the list in 8a) today for your chronic pain condition?

☐ Yes ☐ No

8a) If yes, please select

☐ Medical doctors ☐ Physiotherapist ☐ Chiropractor

☐ Osteopathic practitioner ☐ massage therapist

☐ Other treatments please specify:_____

8b) How much did you spend on these treatments in total today?

$_____

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Form 1 Day Two

1) How intense is your pain at this moment?

No pain at all — Worst pain imaginable

2) What is the highest level of your pain today?

No pain at all — Worst pain imaginable

3) What is the average level of you pain today?

No pain at all — Worst pain imaginable

4) How strong is the average level of your pain today?

20	
19	
18	EXTREME INTENSE
17	VERY INTENSE
16	INTENSE
15	STRONG
14	
13	SLIGHTLY INTENSE
12	BARELY STRONG
11	MODERATE
10	
9	
8	MILD
7	
6	VERY MILD
5	WEAK
4	VERY WEAK
3	
2	
1	FAINT
	NO PAIN SENSATON

5) How unpleasant is the average level of your pain today?

20	
19	
18	
17	VERY INTOLERABLE
16	INTOLERABLE
15	
14	VERY DISTRESSING
13	SLIGHTLY INTOLERABLE
12	VERY ANNOYING
11	DISTRESSING
10	VERY UNPLEASANT
9	SLIGHTLY DISTRESSING
8	ANNOYING
7	UNPLEASANT
6	SLIGHTLY ANNOYING
5	SLIGHTLY UNPLEASANT
4	
3	
2	
1	
0	NEUTRAL

6) When did you feel the pain today?

6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am 2am 4am 6am

7

Code: ☐☐☐☐☐☐☐☐ Date: ☐☐☐☐☐☐☐☐

Pain Medication Taken

Form 2

7) Please put the number associated with the pain medications in the related columns (see the listed pain medications below).

Date	Medication	Medication	Medication	Medication	Medication
Time	Doses Taken	Doses Taken	Doses Taken	Doses Taken	Doses Taken
1-2 am					
3-4 am					
5-6 am					
7-8 am					
9-10 am					
11am-12 pm					
1-2 pm					
3-4 pm					
5-6 pm					
7-8 pm					
9-10 pm					
11pm-12 am					
Total					

List of Pain Medications:

1. Anamorph	2. Dilaudid	3. Durogesic	4. Endone
5. Kapanol	6. MS Contin	7. MS Mono	8. Ordine
9. OxyContin	10. OxyNorm	11. Panadeine	12. Panadeine Forte
13.Pethidine Hydrochloride	14. Physeptone	15. Proladone	16. Tramal
17. Aspirin	18. Celebrex	19. other 1	20. Other 2
21. Other 3	22. Other 4		

8) Did you have any of the following consultations (see the list in 8a) today for your chronic pain condition?

☐ Yes ☐ No

8a) If yes, please select

☐ Medical doctors ☐ Physiotherapist ☐ Chiropractor

☐ Osteopathic practitioner ☐ massage therapist

☐ Other treatments please specify:_____

8b) How much did you spend on these treatments in total today?

$_____

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Form 1 Day Three

1) How intense is your pain **at this moment?**

No pain at all — Worst pain imaginable

2) What is the **highest** level of your pain today?

No pain at all — Worst pain imaginable

3) What is the **average** level of your pain today?

No pain at all — Worst pain imaginable

4) How **strong** is the average level of your pain today?

20	
19	
18	EXTREME INTENSE
17	VERY INTENSE
16	INTENSE
15	STRONG
14	
13	SLIGHTLY INTENSE
12	BARELY STRONG
11	MODERATE
10	
9	
8	MILD
7	
6	VERY MILD
5	WEAK
4	VERY WEAK
3	
2	
1	FAINT
	NO PAIN SENSATON

5) How **unpleasant** is the average level of your pain today?

20	
19	
18	
17	VERY INTOLERABLE
16	INTOLERABLE
15	
14	VERY DISTRESSING
13	SLIGHTLY INTOLERABLE
12	VERY ANNOYING
11	DISTRESSING
10	VERY UNPLEASANT
9	SLIGHTLY DISTRESSING
8	ANNOYING
7	UNPLEASANT
6	SLIGHTLY ANNOYING
5	SLIGHTLY UNPLEASANT
4	
3	
2	
1	
0	NEUTRAL

6) When did you feel the pain today?

6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am 2am 4am 6am

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Medication Taken

Form 2

7) Please put the number associated with the pain medications in the related columns (see the listed pain medications below).

Date	Medication	Medication	Medication	Medication	Medication
Time	Doses Taken	Doses Taken	Doses Taken	Doses Taken	Doses Taken
1-2 am					
3-4 am					
5-6 am					
7-8 am					
9-10 am					
11am-12 pm					
1-2 pm					
3-4 pm					
5-6 pm					
7-8 pm					
9-10 pm					
11pm-12 am					
Total					

List of Pain Medications:

1. Anamorph	2. Dilaudid	3. Durogesic	4. Endone
5. Kapanol	6. MS Contin	7. MS Mono	8. Ordine
9. OxyContin	10. OxyNorm	11. Panadeine	12. Panadeine Forte
13.Pethidine Hydrochloride	14. Physeptone	15. Proladone	16. Tramal
17. Aspirin	18. Celebrex	19. other 1	20. Other 2
21. Other 3	22. Other 4		

8) Did you have any of the following consultations (see the list in 8a) today for your chronic pain condition?

☐ Yes ☐ No

8a) If yes, please select

☐ Medical doctors ☐ Physiotherapist ☐ Chiropractor

☐ Osteopathic practitioner ☐ massage therapist

☐ Other treatments please specify:_____

8b) How much did you spend on these treatments in total today?

$_____

10

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Form 1 Day Four

1) How intense is your pain **at this moment?**

No pain at all — Worst pain imaginable

2) What is the **highest** level of your pain today?

No pain at all — Worst pain imaginable

3) What is the **average** level of your pain today?

No pain at all — Worst pain imaginable

4) How **strong** is the average level of your pain today?

20	
19	
18	EXTREME INTENSE
17	VERY INTENSE
16	INTENSE
15	STRONG
14	
13	SLIGHTLY INTENSE
12	BARELY STRONG
11	MODERATE
10	
9	
8	MILD
7	
6	VERY MILD
5	WEAK
4	VERY WEAK
3	
2	
1	FAINT
	NO PAIN SENSATON

5) How **unpleasant** is the average level of your pain today?

20	
19	
18	
17	VERY INTOLERABLE
16	INTOLERABLE
15	
14	VERY DISTRESSING
13	SLIGHTLY INTOLERABLE
12	VERY ANNOYING
11	DISTRESSING
10	VERY UNPLEASANT
9	SLIGHTLY DISTRESSING
8	ANNOYING
7	UNPLEASANT
6	SLIGHTLY ANNOYING
5	SLIGHTLY UNPLEASANT
4	
3	
2	
1	
0	NEUTRAL

6) When did you feel the pain today?

6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am 2am 4am 6am

11

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Medication Taken

Form 2

7) Please put the number associated with the pain medications in the related columns (see the listed pain medications below).

Date	Medication	Medication	Medication	Medication	Medication
Time	Doses Taken	Doses Taken	Doses Taken	Doses Taken	Doses Taken
1-2 am					
3-4 am					
5-6 am					
7-8 am					
9-10 am					
11am-12 pm					
1-2 pm					
3-4 pm					
5-6 pm					
7-8 pm					
9-10 pm					
11pm-12 am					
Total					

List of Pain Medications:

1. Anamorph	2. Dilaudid	3. Durogesic	4. Endone
5. Kapanol	6. MS Contin	7. MS Mono	8. Ordine
9. OxyContin	10. OxyNorm	11. Panadeine	12. Panadeine Forte
13.Pethidine Hydrochloride	14. Physeptone	15. Proladone	16. Tramal
17. Aspirin	18. Celebrex	19. other 1	20. Other 2
21. Other 3	22. Other 4		

8) Did you have any of the following consultations (see the list in 8a) today for your chronic pain condition?

☐ Yes ☐ No

8a) If yes, please select

☐ Medical doctors ☐ Physiotherapist ☐ Chiropractor

☐ Osteopathic practitioner ☐ massage therapist

☐ Other treatments please specify:_____

8b) How much did you spend on these treatments in total today?

$_____

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Form 1 Day Five

1) How intense is your pain **at this moment?**

No pain at all — Worst pain imaginable

2) What is the **highest** level of your pain today?

No pain at all — Worst pain imaginable

3) What is the **average** level of your pain today?

No pain at all — Worst pain imaginable

4) How **strong** is the average level of your pain today?

20	
19	
18	EXTREME INTENSE
17	VERY INTENSE
16	INTENSE
15	STRONG
14	
13	SLIGHTLY INTENSE
12	BARELY STRONG
11	MODERATE
10	
9	
8	MILD
7	
6	VERY MILD
5	WEAK
4	VERY WEAK
3	
2	
1	FAINT
	NO PAIN SENSATON

5) How **unpleasant** is the average level of your pain today?

20	
19	
18	
17	VERY INTOLERABLE
16	INTOLERABLE
15	
14	VERY DISTRESSING
13	SLIGHTLY INTOLERABLE
12	VERY ANNOYING
11	DISTRESSING
10	VERY UNPLEASANT
9	SLIGHTLY DISTRESSING
8	ANNOYING
7	UNPLEASANT
6	SLIGHTLY ANNOYING
5	SLIGHTLY UNPLEASANT
4	
3	
2	
1	
0	NEUTRAL

6) When did you feel the pain today?

6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am 2am 4am 6am

13

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Medication Taken

Form 2

7) Please put the number associated with the pain medications in the related columns (see the listed pain medications below).

Date	Medication	Medication	Medication	Medication	Medication
Time	Doses Taken	Doses Taken	Doses Taken	Doses Taken	Doses Taken
1-2 am					
3-4 am					
5-6 am					
7-8 am					
9-10 am					
11am-12 pm					
1-2 pm					
3-4 pm					
5-6 pm					
7-8 pm					
9-10 pm					
11pm-12 am					
Total					

List of Pain Medications:

1. Anamorph	2. Dilaudid	3. Durogesic	4. Endone
5. Kapanol	6. MS Contin	7. MS Mono	8. Ordine
9. OxyContin	10. OxyNorm	11. Panadeine	12. Panadeine Forte
13.Pethidine Hydrochloride	14. Physeptone	15. Proladone	16. Tramal
17. Aspirin	18. Celebrex	19. other 1	20. Other 2
21. Other 3	22. Other 4		

8) Did you have any of the following consultations (see the list in 8a) today for your chronic pain condition?

☐ Yes ☐ No

8a) If yes, please select

☐ Medical doctors ☐ Physiotherapist ☐ Chiropractor

☐ Osteopathic practitioner ☐ massage therapist

☐ Other treatments please specify:_____

8b) How much did you spend on these treatments in total today?

$_____

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Form 1 Day Six

1) How intense is your pain **at this moment?**

No pain at all — Worst pain imaginable

2) What is the **highest** level of your pain today?

No pain at all — Worst pain imaginable

3) What is the **average** level of your pain today?

No pain at all — Worst pain imaginable

4) How **strong** is the average level of your pain today?

20	
19	
18	EXTREME INTENSE
17	VERY INTENSE
16	INTENSE
15	STRONG
14	
13	SLIGHTLY INTENSE
12	BARELY STRONG
11	MODERATE
10	
9	
8	MILD
7	
6	VERY MILD
5	WEAK
4	VERY WEAK
3	
2	
1	FAINT
	NO PAIN SENSATON

5) How **unpleasant** is the average level of your pain today?

20	
19	
18	
17	VERY INTOLERABLE
16	INTOLERABLE
15	
14	VERY DISTRESSING
13	SLIGHTLY INTOLERABLE
12	VERY ANNOYING
11	DISTRESSING
10	VERY UNPLEASANT
9	SLIGHTLY DISTRESSING
8	ANNOYING
7	UNPLEASANT
6	SLIGHTLY ANNOYING
5	SLIGHTLY UNPLEASANT
4	
3	
2	
1	
0	NEUTRAL

6) When did you feel the pain today?

6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am 2am 4am 6am

15

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Medication Taken

Form 2

7) Please put the number associated with the pain medications in the related columns (see the listed pain medications below).

Date	Medication	Medication	Medication	Medication	Medication
Time	Doses Taken	Doses Taken	Doses Taken	Doses Taken	Doses Taken
1-2 am					
3-4 am					
5-6 am					
7-8 am					
9-10 am					
11am-12 pm					
1-2 pm					
3-4 pm					
5-6 pm					
7-8 pm					
9-10 pm					
11pm-12 am					
Total					

List of Pain Medications:

1. Anamorph	2. Dilaudid	3. Durogesic	4. Endone
5. Kapanol	6. MS Contin	7. MS Mono	8. Ordine
9. OxyContin	10. OxyNorm	11. Panadeine	12. Panadeine Forte
13.Pethidine Hydrochloride	14. Physeptone	15. Proladone	16. Tramal
17. Aspirin	18. Celebrex	19. other 1	20. Other 2
21. Other 3	22. Other 4		

8) Did you have any of the following consultations (see the list in 8a) today for your chronic pain condition?

☐ Yes ☐ No

8a) If yes, please select

☐ Medical doctors ☐ Physiotherapist ☐ Chiropractor

☐ Osteopathic practitioner ☐ massage therapist

☐ Other treatments please specify:_____

8b) How much did you spend on these treatments in total today?

$_____

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Form 1 Day Seven

1) How intense is your pain **at this moment?**

No pain at all — Worst pain imaginable

2) What is the **highest** level of your pain today?

No pain at all — Worst pain imaginable

3) What is the **average** level of your pain today?

No pain at all — Worst pain imaginable

4) How **strong** is the average level of your pain today?

20	
19	
18	EXTREME INTENSE
17	VERY INTENSE
16	INTENSE
15	STRONG
14	
13	SLIGHTLY INTENSE
12	BARELY STRONG
11	MODERATE
10	
9	
8	MILD
7	
6	VERY MILD
5	WEAK
4	VERY WEAK
3	
2	
1	FAINT
	NO PAIN SENSATON

5) How **unpleasant** is the average level of your pain today?

20	
19	
18	
17	VERY INTOLERABLE
16	INTOLERABLE
15	
14	VERY DISTRESSING
13	SLIGHTLY INTOLERABLE
12	VERY ANNOYING
11	DISTRESSING
10	VERY UNPLEASANT
9	SLIGHTLY DISTRESSING
8	ANNOYING
7	UNPLEASANT
6	SLIGHTLY ANNOYING
5	SLIGHTLY UNPLEASANT
4	
3	
2	
1	
0	NEUTRAL

6) When did you feel the pain today?

6am 8am 10am 12pm 2pm 4pm 6pm 8pm 10pm 12am 2am 4am 6am

17

Code: | | | | | | | | | Date: | | | | | | | | |

Pain Medication Taken

Form 2

7) Please put the number associated with the pain medications in the related columns (see the listed pain medications below).

Date	Medication	Medication	Medication	Medication	Medication
Time	Doses Taken	Doses Taken	Doses Taken	Doses Taken	Doses Taken
1-2 am					
3-4 am					
5-6 am					
7-8 am					
9-10 am					
11am-12 pm					
1-2 pm					
3-4 pm					
5-6 pm					
7-8 pm					
9-10 pm					
11pm-12 am					
Total					

List of Pain Medications:

1. Anamorph	2. Dilaudid	3. Durogesic	4. Endone
5. Kapanol	6. MS Contin	7. MS Mono	8. Ordine
9. OxyContin	10. OxyNorm	11. Panadeine	12. Panadeine Forte
13.Pethidine Hydrochloride	14. Physeptone	15. Proladone	16. Tramal
17. Aspirin	18. Celebrex	19. other 1	20. Other 2
21. Other 3	22. Other 4		

8) Did you have any of the following consultations (see the list in 8a) today for your chronic pain condition?

☐ Yes ☐ No

8a) If yes, please select

☐ Medical doctors ☐ Physiotherapist ☐ Chiropractor

☐ Osteopathic practitioner ☐ massage therapist

☐ Other treatments please specify:_____

8b) How much did you spend on these treatments in total today?

$_____

Code: | | | | | | | | | Date: | | | | | | | | |

Form 3

Side Effects of Pain Medication

(Fill in this form at the end of the week)

The severity of each side effect is defined by the scale below (0 = no symptoms; 10 =very severe symptoms). Please indicate your response.

1. Nausea

0 (No symptom at all) 10 (Very severe)

2. Vomiting

0 (No symptom at all) 10 (Very severe)

3. Dizziness

0 (No symptom at all) 10 (Very severe)

4. Fatigue

0 (No symptom at all) 10 (Very severe)

5. Drowsiness

0 (No symptom at all) 10 (Very severe)

6. Blurred vision

0 (No symptom at all) 10 (Very severe)

7. Sedation

0 (No symptom at all) 10 (Very severe)

8. Lethargy

0 (No symptom at all) 10 (Very severe)

9. Anxiety

0 (No symptom at all) 10 (Very severe)

10. Nightmares

0 (No symptom at all) 10 (Very severe)

11. Constipation

0 (No symptom at all) 10 (Very severe)

12. Other (please describe)

0 (No symptom at all) 10 (Very severe)

Code: | | | | | | | | | Date: | | | | | | | | |

Form 4

Report of Adverse Events for Acupuncture (if applicable)

(Fill in this form at the end of the week)

(Completed by patients)

Please record any unexpected symptoms during or after your acupuncture treatment. **You don't need to fill in the form if you don't have any discomfort. You still need to return this to us even it is not filled in.**

Type of Event	Date	How long does it last	Impact on your life						How do you manage it?
			Not at all (0)	Minimal (1)	Mild (2)	Moderate (3)	Severe (4)	Extremely Severe (5)	
Fainting									
Infection									
Dizziness									
Bruising									
Pain									
Lethargy									
Others									

Appendix 21 Items removed from the test-retest reliability analysis

Domain	Items
Pain quality	Not known
Pain rhythm	Not known
Pain aggravator	Environmental changes-windy days Others-not known For female patient-Before period For female patient-during period For female patient-after period
Pain alleviator	Environmental changes-windy days Others-everything Others-not known Others-other For female patient-Before period For female patient-during period For female patient-after period
Other symptoms	Watery diarrhoea For female patients-abdominal pain during or before periods For female patients-low back pain during or before periods For female patients-dark blood For female patients-light blood (pink) For female patients-bleeding with clots For female patients-excessive bleeding For female patients-light bleeding For female patients-delayed periods For female patients-early periods For female patients-irregular periods For female patients-excessive watery discharge- For female patients-yellow discharge

Appendix 22 Baseline week frequency analysis of pain regions (n=106)

Pain regions	Frequency	Percentage
Head, neck and shoulder regions		
Neck	**48**	**45.30%**
Shoulder	38	35.80%
Shoulder blades	31	29.20%
Back of the head	18	17.00%
Sides of the head	16	15.10%
Frontal head	15	14.20%
Vertex	6	5.70%
Upper limbs		
Upper arm	31	29.20%
Wrist	23	21.70%
Fingers	22	20.80%
Hand	21	19.80%
Elbow	18	17.00%
Forearm	18	17.00%
Lower limbs		
Hip	**46**	**43.40%**

Pain regions	Frequency	Percentage
Knee	**43**	**40.60%**
Thigh	36	34.00%
Calf	33	31.10%
Ankle	32	30.20%
Front of the leg	25	23.60%
Toes	24	22.60%
Sole	19	17.90%
Heel	15	14.20%
Front of the body trunk		
Groin	21	19.80%
Chest	16	15.10%
Side of the body	9	8.50%
Stomach	8	7.50%
Abdomen	8	7.50%
Back of the body trunk		
Lower back	**82**	**77.40%**
Buttocks	40	37.70%
Middle back	36	34.00%
Sacrum	36	34.00%
Between shoulder blades	35	33.00%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 23 Baseline week frequency analysis of pain quality and pain rhythm (n=106)

Pain quality	Frequency	Percentage	Pain rhythm	Frequency	Percentage
Sharp	**62**	**58.50%**	**All the time**	**79**	**74.50%**
Fixed location	**50**	**47.20%**	**Worse at the end of the day**	**45**	**42.50%**
Numbness	39	36.80%	**Worse when first get up**	**43**	**40.60%**
Dull pain with weakness	36	34.00%	Fluctuate	28	26.40%
Burning	35	33.00%	Worse in the afternoon	22	20.80%
Dull	28	26.40%	Worse during the day, better at night	18	17.00%
Moving from one spot to another	23	21.70%	Worse at night, better during the day	18	17.00%
Hot	22	20.80%	Worse in the morning	8	7.50%
Pulling	21	19.80%	*Worse at lunch time*	*4*	*3.80%*
Pricking	20	18.90%	*Recurrent*	*1*	*0.90%*
Cold	11	10.40%	*Not known*	*0*	*0%*
Distending	11	10.40%			
Not known	*1*	*0.90%*			

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 24 Baseline week frequency analysis of pain aggravator (n=106)

Pain aggravator	Frequency	Percentage
Environmental changes		
Cold weather	**58**	**54.70%**
Weather change	28	26.40%
Hot weather	22	20.80%
Wet weather	11	10.40%
Windy days	9	8.50%
Exercises of sporting		
Standing	**69**	**65.10%**
Physical work	**68**	**64.20%**
Walking	**66**	**62.30%**
Lifting	**57**	**53.80%**
Sitting	**55**	**51.90%**
Going up/down stairs	**54**	**50.90%**
Bending	**53**	**50.00%**
Driving	40	37.70%
Any movement	28	26.40%
Lying down	22	20.80%
Physiological and psychic changes		
Stress	**59**	**55.70%**
Bad night sleep	**56**	**52.80%**
Being emotional	42	39.60%
Being hungry	9	8.50%
After eating	*2*	*1.90%*
Others		
Household chores	**53**	**50.00%**
Pressure on the area	36	34.00%
Everything	26	24.50%
Sex	20	18.90%
Not known	*0*	*0%*
For female patients (n=15)		
Before period	**6**	**40.0%**
During period	**6**	**40.0%**
After period	1	6.70%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 25 Baseline week frequency analysis of pain alleviator (n=106)

Pain alleviators	Frequency	Percentage
Environmental changes		
Hot packs	**57**	**53.80%**
Warm/hot shower	**45**	**42.50%**
Warm/hot bath	31	29.20%
Hot weather	16	15.10%
Cold packs	9	8.50%
Cold weather	*3*	*2.80%*
Wet weather	*1*	*0.90%*

Pain alleviators	Frequency	Percentage
Windy days	*0*	*0%*
Exercises of sporting		
Resting	**47**	**44.30%**
Lying down	41	38.70%
Gentle massage	39	36.80%
Gentle exercise	26	24.50%
Walking	20	18.90%
Sitting	13	12.30%
Any movement	9	8.50%
Driving	*5*	*4.70%*
Standing	*3*	*2.80%*
Physiological and psychic changes		
Pain killer	**85**	**80.20%**
Keeping my mind off pain	39	36.80%
Sleep	33	31.10%
Being with other people	25	23.60%
Deep breathing	21	19.80%
Watching TV	19	17.90%
Pressure on the pain area	14	13.20%
Bowel movement	12	11.30%
Reading	12	11.30%
Alcohol	10	9.40%
Eating	*4*	*3.80%*
Belching	*3*	*2.80%*
Working	*3*	*2.80%*
Being hungry	*1*	*0.90%*
Others		
Keeping busy	33	31.10%
Nothing	11	10.40%
Household chores	6	5.70%
Sex	*2*	*1.90%*
Everything	*2*	*1.90%*
Not known	*0*	*0%*
For female patients (n=15)		
During period	4	26.7%
After period	*0*	*0%*
Before period	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 26 Baseline week frequency analysis of other symptoms (n=106)

Other symptoms	Frequency	Percentage
Feeling tired easily	**70**	**66.00%**
Insomnia	**57**	**53.80%**
Limited movement	**55**	**51.90%**
Poor concentration	**53**	**50.00%**
Poor memory	**53**	**50.00%**
Feeling depressed	**48**	**45.30%**

Other symptoms	Frequency	Percentage
Low libido	**46**	**43.40%**
Constipation	**44**	**41.50%**
Night sweating	42	39.60%
Irritable	42	39.60%
Feeling hot easily	41	38.70%
Feeling cold easily	37	34.90%
Swollen joints	35	33.00%
Sweat upon mild activities	34	32.10%
Feeling nervous easily	34	32.10%
Dizziness	33	31.10%
Frequent urination at night	30	28.30%
Skin itch	29	27.40%
Cold hands and feet	28	26.40%
Thirsty	28	26.40%
Nausea	28	26.40%
Poor appetite	27	25.50%
Dry or sore throat	25	23.60%
Frequent urination	25	23.60%
Short of breath	25	23.60%
Dry skin	23	21.70%
Heavy sensation in the body	22	20.80%
Sigh often	22	20.80%
Reflux	22	20.80%
Need deep breathing	19	17.90%
Flushed face	17	16.00%
Red and hot joints	16	15.10%
Leak when sneezing or cough	16	15.10%
Abdominal distention	15	14.20%
Indigestion	14	13.20%
Cold joints	11	10.40%
Cold lower back or knees	11	10.40%
Dry stools	11	10.40%
Stuffiness in the chest	11	10.40%
Distension sensation in the abdomen	10	9.40%
Catch cold easily	9	8.50%
Mushy stools	8	7.50%
Hot palms	6	5.70%
Belching	*5*	*4.70%*
Watery diarrhoea	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 27 Baseline week frequency analysis of gynaecological symptoms for female participants (n=15)

Gynaecological symptoms	Frequency	Percentage
Abdominal pain during or before periods	5	33.30%
Low back pain during or before periods	5	33.30%
Dark blood	5	33.30%
Irregular periods	3	20.00%
Excessive bleeding	2	13.30%
Bleeding with clots	2	13.30%
Light bleeding	1	6.70%
Delayed periods	1	6.70%
Yellow discharge	*0*	*0%*
Light blood (pink)	*0*	*0%*
Early periods	*0*	*0%*
Excessive watery discharge	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 28 List of sham acupoints and their location

Sham acupuncture points for each real acupuncture points	Description of location
Medial volar aspects of the forearm	
Hegu (L14)	With palm facing the chest, the point is located eight body units distal to the olecranon between the Heart and Small Intestine meridians. Needle is inserted perpendicularly.
Shousanli (LI10)	On the medial aspect of the forearm, four body units proximal to sham LI4.
Zhigou (TE6)	On the medial surface of the forearm, five body units distal to the olecranon, between sham LI10 and LI4.
Dorsal lateral aspect of the forearm	
Shenmen (HT7)	On the dorsal lateral aspect of the forearm, six body units distal to the lateral epicondyle.
Yinxi (HT6)	Two body units proximal to sham HT7.
Neiguan (PC6)	Two body units proximal to sham HT6 (Four body units proximal to sham HT7).
Lateral aspect of the leg	
Zusanli (ST36)	On the lateral aspect of the leg, two body units anterior and two body units proximal to BL58 (Feiyang), i.e. two body units proximal to sham ST40.
Fenglong (ST40)	On the lateral aspect of the leg, two body units anterior to BL58 (Feiyang).
Medial aspect of leg	
Taixi (KI3)	One body unit directly proximal to the real acupoint KI7 (Fuliu) and one body unit posterior.
Fuliu (KI7)	Two body unit directly proximal to the real acupoint and one body unit posterior (one body unit proximal to sham KI3).
Sanyinjiao (SP6)	On the medial aspect of the leg, four body units distal to the medial end of the popliteal crease.

Sham acupuncture points for each real acupuncture points	Description of location
Yinlingquan (SP9)	Three body units distal to the medial end of the popliteal crease.
Anterior aspect of the thigh	
Xuehai (SP10)	Two body units proximal to the upper mid point of the boarder of the patella.
Head	
Baihui (GV20)	1.5 cm above and lateral to Yintang (EX-NH 3) between GB and BL meridians.
Yintang (EX-NH 3).	1.5 cm above and lateral to Yintang (EX-NH 3) between GB and BL meridians. Same as sham GV20. Only use unilateral point. When both GV20 and Yintang are needled, only use one sham point. .
Back	
Geshu (BL17)	Four body units lateral to the spinous process of the sixth thoracic vertebrae.
Feishu (BL13)	Four body units lateral spinous process of the T3.
Abdomen	
Tianshu (ST25)	One body unit lateral and one body unit proximal to the umbilicus.
GuanYuan (CV4)	Four body units later to the real point on either side.

Appendix 29 Association of CM patterns and outcome measures

Multivariate Tests[a]							
Effect		**Value**	**F**	**Hypothesis df**	**Error df**	**Sig.**	**Partial Eta Squared**
Intercept	Pillai's Trace	0.984	802.988 [b]	4.000	52.000	0.000	0.984
	Wilks' Lambda	0.016	802.988 [b]	4.000	52.000	0.000	0.984
	Hotelling's Trace	61.768	802.988 [b]	4.000	52.000	0.000	0.984
	Roy's Largest Root	61.768	802.988 [b]	4.000	52.000	0.000	0.984
Clusters	Pillai's Trace	0.197	3.199 [b]	4.000	52.000	0.020	0.197
	Wilks' Lambda	0.803	3.199 [b]	4.000	52.000	0.020	0.197
	Hotelling's Trace	0.246	3.199 [b]	4.000	52.000	0.020	0.197
	Roy's Largest Root	0.246	3.199 [b]	4.000	52.000	0.020	0.197
Tests of Between-Subjects Effects							
Source	**Dependent Variable**	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**	**Partial Eta Squared**
Clusters	Average of OM at baseline weeks	296546.893	1	296546.893	1.017	0.318	0.018
	Average of average intensity of baseline weeks	1.413	1	1.413	0.342	0.561	0.006
	Total score of BDI at baseline week	973.728	1	973.728	10.426	0.002	0.159
	Total SF36 score at baseline week	3060.285	1	3060.285	8.752	0.005	0.137
CM heat pattern and CM cold with deficiency pattern							

Dependent Variable	CM patterns	N	Mean	Std. Error	95% Confidence Interval	
					Lower Bound	Upper Bound
Average of OM at baseline weeks	CM heat pattern	30	445.268	98.595	247.679	642.857
	CM cold with deficiency pattern	27	589.726	103.928	381.449	798.003
Average of average intensity of baseline weeks	CM heat pattern	30	5.451	0.371	4.708	6.194
	CM cold with deficiency pattern	27	5.136	0.391	4.352	5.919
Total score of BDI at baseline week	CM heat pattern	30	16.167	1.764	12.631	19.703
	CM cold with deficiency pattern	27	24.444	1.860	20.717	28.172
Total SF36 score at baseline week	CM heat pattern	30	45.933	3.414	39.091	52.774
	CM cold with deficiency pattern	27	31.258	3.599	24.046	38.470

a. Exact statistic

b. Exact statistic

BDI: Beck depression inventory

CM: Chinese medicine

OM: Opioid medication

SF36: Medical outcome short for health survey 36 items

Appendix 30 Summary of frequency analysis of baseline week and end of treatment week

Domain	Symptoms	REA		SEA		PMM alone	
		Baseline week (n=45)	End of treatment week (n=28)	Baseline week (n=28)	End of treatment week (n=23)	Baseline week (n=28)	End of treatment week (n=17)
Pain regions	Lower back	77.86%	71.40%	75.00%	78.30%	82.00%	88.20%
	Hip	42.20%		46.40%	52.20%	42.90%	41.20%
	Neck	42.20%		60.70%	65.20%		
	Knee			46.40%	52.20%		52.90%
	Between blades			42.90%	47.80%		41.20%
	Calf						41.20%
	Middle back			42.90%			
	Front of the leg			42.90%			41.20%
	Hand				43.50%		
	Ankle			42.90%			
	Sacrum						41.20%
	Shoulder			50.00%	65.20%		41.20%
	Buttocks			50.00%			
	Thigh			46.40%	52.20%		41.2%,
	Upper arm			50.00%			
Pain quality	Sharp	62.20%	46.40%	60.70%	52.20%	53.60%	64.70%
	Fixed location	48.90%		53.60%		42.90%	47.10%
	Burning		42.90%				41.20%
	Dull pain with weakness				43.50%	46.40%	
	Numbness			42.90%			
Pain rhythm	All the time	77.80%	60.70%	82.10%	65.20%	71.40%	64.70%
	Worse when first get up	44.40%					
	Worse at the end of the day	44.40%		42.90%			41.20%
	Worse at night, better during the day				43.50%		
Pain aggravator	Physical work	66.70%	60.70%	64.30%	65.20%	60.70%	58.80%
	Standing	66.70%	64.30%	57.10%	60.90%	71.40%	76.50%
	Walking	66.70%	46.40%	50.00%	56.50%	64.30%	64.70%
	Household	60.00%	42.90%	46.40%	47.80%		47.10%

Domain	Symptoms	REA		SEA		PMM alone	
		Baseline week (n=45)	End of treatment week (n=28)	Baseline week (n=28)	End of treatment week (n=23)	Baseline week (n=28)	End of treatment week (n=17)
	chores						
	Cold weather	57.80%	46.40%	42.90%	78.30%	60.70%	76.50%
	Sitting	53.30%	53.60%	57.10%	52.20%	46.40%	47.10%
	Bending	51.10%	53.60%	42.90%	47.80%	50.00%	47.10%
	Lifting	51.10%	53.60%	53.60%	56.50%	60.70%	58.80%
	Stress	51.10%	50.00%	60.70%	52.20%	53.60%	35.30%
	Going up/down stairs	48.90%	42.90%			64.30%	58.80%
	Driving	48.90%					
	Bad night sleep	46.70%	50.00%	57.10%	65.20%	60.70%	41.20%
	Pressure on the area	46.70%					
	Being emotional			46.40%			
Pain alleviator	Pain killer	88.90%	85.70%	71.40%	73.90%	78.60%	
	Resting	48.90%	46.40%			46.40%	41.20%
	Lying down	44.40%					41.20%
	Hot packs	42.20%	57.10%	71.40%	78.30%	53.60%	64.70%
	Keeping my mind off pain	40.00%	46.40%		52.20%	46.40%	
	Warm/hot shower			50.00%	60.90%		52.90%
	Keeping busy				43.5%,		
	Gentle massage					46.40%	
Other symptoms	Feeling tired easily	62.20%	60.70%	71.40%	82.60%	71.40%	64.70%
	Insomnia	55.60%	53.60%	53.60%		46.40%	52.90%
	Low libido	53.30%				46.40%	47.10%
	Feeling depressed	48.90%		42.90%	52.20%	46.40%	47.10%
	Limited movement	46.70%	50.00%	50.00%	52.20%	64.30%	47.10%
	Constipation	46.70%		42.90%			41.20%
	Poor concentration	44.40%	42.90%	57.10%	56.50%	57.10%	52.90%
	Night	44.40%	46.40%				41.20%

Domain	Symptoms	REA		SEA		PMM alone	
		Baseline week (n=45)	End of treatment week (n=28)	Baseline week (n=28)	End of treatment week (n=23)	Baseline week (n=28)	End of treatment week (n=17)
	sweating						
	Feeling hot easily	42.20%					
	Poor memory	40.00%	42.90%	57.10%	47.80%	60.70%	47.10%
	Nausea			42.90%			
	Feeling cold easily			46.40%	47.80%		41.20%
	Feeling nervous easily			42.90%	52.20%		
	Irritable		42.90%	46.40%	47.80%	42.90%	52.90%
	Thirsty				43.50%		
	Dizziness			46.40%			

Empty cell means percentage of symptom not over 40%

Appendix 31 Baseline week pain region frequency – REA (n=45)

Pain regions	Frequency	Percentage
Head, neck and shoulder regions		
Neck	**19**	**42.20%**
Shoulder blades	12	26.70%
Shoulder	11	24.40%
Frontal head	7	15.60%
Back of the head	7	15.60%
Sides of the head	6	13.30%
Vertex	4	8.90%
Upper limbs		
Upper arm	10	22.20%
Fingers	8	17.80%
Hand	7	15.60%
Forearm	6	13.30%
Wrist	6	13.30%
Elbow	4	8.90%
Lower limbs		
Hip	**19**	**42.20%**
Knee	16	35.60%
Calf	15	33.30%
Thigh	13	28.90%
Ankle	11	24.40%
Toes	8	17.80%
Sole	6	13.30%
Front of the leg	5	11.10%
Heel	5	11.10%
Front of the body trunk		

Pain regions	Frequency	Percentage
Groin	10	22.20%
Chest	5	11.10%
Abdomen	4	8.90%
Stomach	3	6.70%
Side of the body	3	6.70%
Back of the body trunk		
Lower back	**35**	**77.80%**
buttocks	15	33.30%
Between shoulder blades	14	31.10%
Middle back	13	28.90%
Sacrum	13	28.90%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 32 Baseline week pain quality and rhythm frequency – REA (n=45)

Pain quality	Frequency	Percentage	Pain rhythm	Frequency	Percentage
Sharp	**28**	**62.20%**	**All the time**	**35**	**77.80%**
Fixed location	**22**	**48.90%**	**Worse when first get up**	**20**	**44.40%**
Burning	17	37.80%	**Worse at the end of the day**	**20**	**44.40%**
Numbness	15	33.30%	Fluctuate	13	28.90%
Hot	14	31.10%	Worse in the afternoon	10	22.20%
Pulling	11	24.40%	Worse during the day, better at night	7	15.60%
Moving from one spot to another	11	24.40%	Worse at night, better during the day	4	8.90%
Dull	11	24.40%	*Worse in the morning*	*2*	*4.40%*
Dull pain with weakness	11	24.40%	*Recurrent*	*1*	*2.20%*
Pricking	9	20.00%	*Worse at lunch time*	*1*	*2.20%*
Cold	4	8.90%	*Not known*	*0*	*0%*
Distending	3	6.70%			
Not known	*0*	*0%*			

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 33 Baseline week pain aggravator frequency – REA (n=45)

Pain aggravator	Frequency	Percentage
Environmental changes		
Cold weather	**26**	**57.80%**
Weather change	11	24.40%
Hot weather	11	24.40%
Wet weather	4	8.90%
Windy days	4	8.90%
Exercises of sporting		
Standing	**30**	**66.70%**
Walking	**30**	**66.70%**
Physical work	**30**	**66.70%**
Sitting	**24**	**53.30%**
Lifting	**23**	**51.10%**
Bending	**23**	**51.10%**
Going up/down stairs	**22**	**48.90%**
Driving	**22**	**48.90%**
Lying down	9	20.00%
Any movement	8	17.80%
Physiological and psychic changes		
Stress	**23**	**51.10%**
Bad night sleep	**21**	**46.70%**
Being emotional	15	33.30%
Being hungry	4	8.90%
After eating	*1*	*2.20%*
Others		
Household chores	**27**	**60.00%**
Pressure on the area	**21**	**46.70%**
Sex	11	24.40%
Everything	9	20.00%
Not known	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 34 Baseline week pain alleviator frequency – REA (n=45)

Pain alleviator	Frequency	Percentage
Environmental changes		
Hot packs	**19**	**42.20%**
Warm/hot shower	17	37.80%
Warm/hot bath	12	26.70%
Cold packs	5	11.10%
Hot weather	5	11.10%
Cold weather	*2*	*4.40%*
Wet weather	*1*	*2.20%*
Windy days	*0*	*0%*
Exercises of sporting		
Resting	**22**	**48.90%**
Lying down	**20**	**44.40%**
Gentle massage	12	26.70%
Gentle exercise	9	20.00%
Walking	7	15.60%
Any movement	5	11.10%
Sitting	4	8.90%
Standing	*2*	*4.40%*
Driving	*1*	*2.20%*
Physiological and psychic changes		
Pain killer	**40**	**88.90%**
Keeping my mind off pain	**18**	**40.00%**
Sleep	15	33.30%
Deep breathing	10	22.20%
Being with other people	10	22.20%
Watching TV	7	15.60%
Pressure on the pain area	5	11.10%
Reading	5	11.10%
Bowel movement	4	8.90%
Alcohol	4	8.90%
Eating	3	6.70%
Working	*2*	*4.40%*
Belching	*1*	*2.20%*
Being hungry	*0*	*0%*
Others		
Keeping busy	15	33.30%
Nothing	6	13.30%
Household chores	4	8.90%
Sex	*0*	*0%*
Everything	*0*	*0%*
Not known	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 35 Baseline week other pain accompanying symptom frequency – REA (n=45)

Item	Frequency	Percentage
Feeling tired easily	**28**	**62.20%**
Insomnia	**25**	**55.60%**
Low libido	**24**	**53.30%**
Feeling depressed	**22**	**48.90%**
Limited movement	**21**	**46.70%**
Constipation	**21**	**46.70%**
Night sweating	**20**	**44.40%**
Poor concentration	**20**	**44.40%**
Feeling hot easily	**19**	**42.20%**
Poor memory	**18**	**40.00%**
Feeling cold easily	17	37.80%
Irritable	16	35.60%
Sweat upon mild activities	14	31.10%
Feeling nervous easily	14	31.10%
Swollen joints	13	28.90%
Thirsty	13	28.90%
Frequent urination at night	13	28.90%
Dry skin	12	26.70%
Poor appetite	12	26.70%
Reflux	12	26.70%
Skin itch	12	26.70%
Cold hands and feet	11	24.40%
Nausea	11	24.40%
Dizziness	10	22.20%
Heavy sensation in the body	9	20.00%
Dry or sore throat	9	20.00%
Frequent urination	9	20.00%
Need deep breathing	8	17.80%
Short of breath	8	17.80%
Indigestion	7	15.60%
Flushed face	7	15.60%
Leak when sneezing or cough	7	15.60%
Sigh often	7	15.60%
Red and hot joints	6	13.30%
Cold joints	5	11.10%
Distention sensation in the abdomen	5	11.10%
Catch cold easily	5	11.10%
Abdominal distention	5	11.10%
Mushy stools	4	8.90%
Stuffiness in the chest	4	8.90%
Cold lower back or knees	3	6.70%
Hot palms	3	6.70%
Belching	3	6.70%
Dry stools	*1*	*2.20%*
Watery diarrhoea	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 36 Baseline week pain region frequency – SEA (n=28)

Pain regions	Frequency	Percentage
Head, neck and shoulder regions		
Neck	**17**	**60.70%**
Shoulder	**14**	**50.00%**
Shoulder blades	10	35.70%
Back of the head	8	28.60%
Sides of the head	4	14.30%
Frontal head	3	10.70%
Vertex	2	7.10%
Upper limbs		
Upper arm	**14**	**50.00%**
Elbow	10	35.70%
Wrist	10	35.70%
Fingers	10	35.70%
Forearm	9	32.10%
Hand	8	28.60%
Lower limbs		
Hip	**13**	**46.40%**
Thigh	**13**	**46.40%**
Knee	**13**	**46.40%**
Front of the leg	**12**	**42.90%**
Ankle	**12**	**42.90%**
Calf	9	32.10%
Toes	8	28.60%
Heel	5	17.90%
Sole	5	17.90%
Front of the body trunk		
Chest	8	28.60%
Groin	3	10.70%
Side of the body	3	10.70%
Stomach	*1*	*3.60%*
Abdomen	*1*	*3.60%*
Back of the body trunk		
Lower back	**21**	**75.00%**
Buttocks	**14**	**50.00%**
Between shoulder blades	**12**	**42.90%**
Middle back	**12**	**42.90%**
Sacrum	11	39.30%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 37 Baseline week pain quality and rhythm frequency – SEA (n=28)

Pain quality	Frequency	Percentage	Pain rhythm	Frequency	Percentage
Sharp	**17**	**60.70%**	**All the time**	**23**	**82.10%**
Fixed location	**15**	**53.60%**	**Worse at the end of the day**	**12**	**42.90%**
Numbness	**12**	**42.90%**	Worse when first get up	9	32.10%

Pain quality	Frequency	Percentage	Pain rhythm	Frequency	Percentage
Dull pain with weakness	10	35.70%	Worse at night, better during the day	8	28.60%
Dull	9	32.10%	Fluctuate	7	25.00%
Burning	7	25.00%	Worse during the day, better at night	6	21.40%
Pricking	6	21.40%	Worse in the afternoon	6	21.40%
Cold	5	17.90%	Worse in the morning	4	14.30%
Pulling	5	17.90%	Worse at lunch time	3	10.70%
Distending	5	17.90%	*Recurrent*	*0*	*0%*
Moving from one spot to another	5	17.90%	*Not known*	*0*	*0%*
Hot	3	10.70%			
Not known	*0*	*0%*			

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 38 Baseline week pain aggravator frequency – SEA (n=28)

Pain aggravator	Frequency	Percentage
Environmental changes		
Cold weather	**12**	**42.90%**
Weather change	8	28.60%
Hot weather	5	17.90%
Wet weather	3	10.70%
Windy days	2	7.10%
Exercises of sporting		
Physical work	**18**	**64.30%**
Standing	**16**	**57.10%**
Sitting	**16**	**57.10%**
Lifting	**15**	**53.60%**
Walking	**14**	**50.00%**
Bending	**12**	**42.90%**
Lying down	11	39.30%
Going up/down stairs	11	39.30%
Any movement	8	28.60%
Driving	7	25.00%
Physiological and psychic changes		
Stress	**17**	**60.70%**
Bad night sleep	**16**	**57.10%**
Being emotional	**13**	**46.40%**
Being hungry	2	7.10%
After eating	*1*	*3.60%*
Others		
Household chores	**13**	**46.40%**

Pain aggravator	Frequency	Percentage
Everything	7	25.00%
Pressure on the area	6	21.40%
Sex	4	14.30%
Not known	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 39 Baseline week pain alleviator frequency – SEA (n=28)

Pain alleviators	Frequency	Percentage
Environmental changes		
Hot packs	**20**	**71.40%**
Warm/hot shower	**14**	**50.00%**
Warm/hot bath	10	35.70%
Hot weather	4	14.30%
Cold packs	2	7.10%
Cold weather	*1*	*3.60%*
Wet weather	*0*	*0%*
Windy days	*0*	*0%*
Exercises of sporting		
Gentle massage	11	39.30%
Gentle exercise	10	35.70%
Lying down	9	32.10%
Resting	9	32.10%
Walking	7	25.00%
Sitting	6	21.40%
Standing	*1*	*3.60%*
Any movement	*1*	*3.60%*
Driving	*1*	*3.60%*
Physiological and psychic changes		
Pain killer	**20**	**71.40%**
Keeping my mind off pain	8	28.60%
Being with other people	8	28.60%
Sleep	8	28.60%
Deep breathing	6	21.40%
Pressure on the pain area	6	21.40%
Watching TV	6	21.40%
Alcohol	3	10.70%
Reading	3	10.70%
Belching	*1*	*3.60%*
Bowel movement	*1*	*3.60%*
Working	*1*	*3.60%*
Eating	*0*	*0%*
Being hungry	*0*	*0%*
Others		
Keeping busy	7	25.00%
Nothing	4	14.30%
Household chores	2	7.10%
Sex	*1*	*3.60%*

Pain alleviators	Frequency	Percentage
Everything	*1*	*3.60%*
Not known	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 40 Baseline week other pain accompanying symptom frequency – SEA (n=28)

Item	Frequency	Percentage
Feeling tired easily	**20**	**71.40%**
Poor concentration	**16**	**57.10%**
Poor memory	**16**	**57.10%**
Insomnia	**15**	**53.60%**
Limited movement	**14**	**50.00%**
Feeling cold easily	**13**	**46.40%**
Irritable	**13**	**46.40%**
Dizziness	**13**	**46.40%**
Constipation	**12**	**42.90%**
Feeling nervous easily	**12**	**42.90%**
Feeling depressed	**12**	**42.90%**
Nausea	**12**	**42.90%**
Swollen joints	11	39.30%
Cold hands and feet	11	39.30%
Feeling hot easily	11	39.30%
Night sweating	11	39.30%
Dry or sore throat	9	32.10%
Thirsty	9	32.10%
Poor appetite	8	28.60%
Short of breath	8	28.60%
Skin itch	8	28.60%
Heavy sensation in the body	7	25.00%
Low libido	7	25.00%
Sweat upon mild activities	7	25.00%
Dry skin	6	21.40%
Frequent urination at night	6	21.40%
Frequent urination	6	21.40%
Sigh often	6	21.40%
Reflux	6	21.40%
Red and hot joints	5	17.90%
Cold lower back or knees	5	17.90%
Dry stools	5	17.90%
Need deep breathing	5	17.90%
Abdominal distention	5	17.90%
Stuffiness in the chest	5	17.90%
Indigestion	4	14.30%
Flushed face	4	14.30%
Cold joints	3	10.70%
Distention sensation in the abdomen	3	10.70%
Hot palms	3	10.70%
Leak when sneezing or cough	3	10.70%

Item	Frequency	Percentage
Mushy stools	*1*	*3.60%*
Catch cold easily	*1*	*3.60%*
Watery diarrhoea	*0*	*0%*
Belching	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 41 Baseline week pain region frequency – PMM alone (n=28)

Pain regions	Frequency	Percentage
Head, neck and shoulder regions		
Neck	11	39.30%
Shoulder	11	39.30%
Shoulder blades	9	32.10%
Sides of the head	6	21.40%
Frontal head	5	17.90%
Back of the head	3	10.70%
Vertex	*0*	*0%*
Upper limbs		
Upper arm	6	21.40%
Wrist	6	21.40%
Elbow	4	14.30%
Hand	4	14.30%
Fingers	4	14.30%
Forearm	2	7.10%
Lower limbs		
Hip	**12**	**42.90%**
Knee	11	39.30%
Thigh	10	35.70%
Ankle	9	32.10%
Front of the leg	7	25.00%
Calf	7	25.00%
Sole	7	25.00%
Toes	7	25.00%
Heel	4	14.30%
Front of the body trunk		
Groin	8	28.60%
Stomach	4	14.30%
Chest	3	10.70%
Abdomen	3	10.70%
Side of the body	3	10.70%
Back of the body trunk		
Lower back	**23**	**82.10%**
Sacrum	11	39.30%
Middle back	10	35.70%
buttocks	10	35.70%
Between shoulder blades	8	28.60%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 42 Baseline week pain quality and rhythm frequency – PMM alone (n=28)

Pain quality	Frequency	Percentage	Pain rhythm	Frequency	Percentage
Sharp	**15**	**53.60%**	**All the time**	**20**	**71.40%**
Dull pain with weakness	**13**	**46.40%**	Worse when first get up	11	39.30%
Fixed location	**12**	**42.90%**	Worse at the end of the day	11	39.30%
Numbness	11	39.30%	Fluctuate	6	21.40%
Burning	11	39.30%	Worse during the day, better at night	5	17.90%
Moving from one spot to another	6	21.40%	Worse at night, better during the day	5	17.90%
Dull	6	21.40%	Worse in the afternoon	5	17.90%
Pricking	5	17.90%	Worse in the morning	2	7.10%
Pulling	4	14.30%	*Recurrent*	*0*	*0%*
Hot	4	14.30%	*Worse at lunch time*	*0*	*0%*
Distending	3	10.70%	*Not known*	*0*	*0%*
Cold	2	7.10%			
Not known	*1*	*3.60%*			

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 43 Baseline week pain aggravator frequency – PMM alone (n=28)

Pain aggravators	Frequency	Percentage
Environmental changes		
Cold weather	**17**	**60.70%**
Weather change	7	25.00%
Hot weather	5	17.90%
Wet weather	3	10.70%
Windy days	3	10.70%
Exercises of sporting		
Standing	**20**	**71.40%**
Walking	**18**	**64.30%**
Going up/down stairs	**18**	**64.30%**
Physical work	**17**	**60.70%**
Lifting	**17**	**60.70%**
Bending	**14**	**50.00%**
Sitting	**13**	**46.40%**
Any movement	10	35.70%
Driving	10	35.70%
Lying down	*1*	*3.60%*
Physiological and psychic changes		
Bad night sleep	**17**	**60.70%**
Stress	**15**	**53.60%**

Being emotional	11	39.30%
Being hungry	3	10.70%
After eating	*0*	*0%*
Others		
Household chores	11	39.30%
Pressure on the area	9	32.10%
Everything	9	32.10%
Sex	4	14.30%
Not known	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 44 Baseline week pain alleviator frequency – PMM alone (n=28)

Pain alleviators	Frequency	Percentage
Environmental changes		
Hot packs	**15**	**53.60%**
Warm/hot shower	10	35.70%
Warm/hot bath	8	28.60%
Hot weather	6	21.40%
Cold packs	2	7.10%
Cold weather	*0*	*0%*
Wet weather	*0*	*0%*
Windy days	*0*	*0%*
Exercises of sporting		
Gentle massage	**13**	**46.40%**
Resting	**13**	**46.40%**
Lying down	11	39.30%
Gentle exercise	6	21.40%
Walking	5	17.90%
Any movement	3	10.70%
Sitting	2	7.10%
Driving	2	7.10%
Standing	*0*	*0%*
Physiological and psychic changes		
Pain killer	**22**	**78.60%**
Keeping my mind off pain	**13**	**46.40%**
Sleep	9	32.10%
Bowel movement	6	21.40%
Deep breathing	5	17.90%
Being with other people	5	17.90%
Watching TV	5	17.90%
Reading	4	14.30%
Pressure on the pain area	2	7.10%
Alcohol	2	7.10%
Eating	*1*	*3.60%*
Being hungry	*1*	*3.60%*
Belching	*1*	*3.60%*
Working	*0*	*0%*

Others		
Keeping busy	10	35.70%
Sex	*1*	*3.60%*
Everything	*1*	*3.60%*
Nothing	*1*	*3.60%*
Household chores	*0*	*0%*
Not known	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 45 Baseline week other pain accompanying symptom frequency – PMM alone (n=28)

Item	Frequency	Percentage
Feeling tired easily	**20**	**71.40%**
Limited movement	**18**	**64.30%**
Poor memory	**17**	**60.70%**
Poor concentration	**16**	**57.10%**
Insomnia	**13**	**46.40%**
Low libido	**13**	**46.40%**
Feeling depressed	**13**	**46.40%**
Irritable	**12**	**42.90%**
Sweat upon mild activities	11	39.30%
Swollen joints	9	32.10%
Feeling hot easily	9	32.10%
Night sweating	9	32.10%
Constipation	9	32.10%
Frequent urination	9	32.10%
Dizziness	9	32.10%
Frequent urination at night	8	28.60%
Sigh often	8	28.60%
Short of breath	8	28.60%
Poor appetite	7	25.00%
Feeling nervous easily	7	25.00%
Skin itch	7	25.00%
Heavy sensation in the body	6	21.40%
Feeling cold easily	6	21.40%
Dry or sore throat	5	17.90%
Flushed face	5	17.90%
Thirsty	5	17.90%
Dry stools	5	17.90%
Dry skin	5	17.90%
Leak when sneezing or cough	5	17.90%
Need deep breathing	5	17.90%
Nausea	5	17.90%
Cold hands and feet	4	14.30%
Abdominal distention	4	14.30%
Reflux	4	14.30%
Red and hot joints	3	10.70%
Indigestion	3	10.70%

Item	Frequency	Percentage
Cold lower back or knees	3	10.70%
Mushy stools	3	10.70%
Cold joints	2	7.10%
Distention sensation in the abdomen	2	7.10%
Catch cold easily	2	7.10%
Stuffiness in the chest	2	7.10%
Belching	2	7.10%
Hot palms	*0*	*0%*
Watery diarrhoea	*0*	*0%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 46 End of treatment week pain region frequency – REA (n=28)

Pain regions	Frequency	Percentage
Head and shoulder regions		
Neck	9	32.10%
Shoulder blades	9	32.10%
Shoulder	8	28.60%
Frontal head	5	17.90%
Back of the head	3	10.70%
Sides of the head	2	7.10%
Vertex	*0*	*0.00%*
Upper limb		
Wrist	6	21.40%
Hand	5	17.90%
Fingers	5	17.90%
Upper arm	4	14.30%
Elbow	*1*	*3.60%*
Forearm	*1*	*3.60%*
Lower limb		
Hip	11	39.30%
Knee	9	32.10%
Thigh	8	28.60%
Calf	6	21.40%
Toes	6	21.40%
Ankle	5	17.90%
Heel	5	17.90%
Sole	5	17.90%
Front of the leg	4	14.30%
Front of the body		
Groin	6	21.40%
Abdomen	4	14.30%
Side of the body	3	10.70%
Chest	2	7.10%
Stomach	1	3.60%
Back of the body		
Lower back	20	71.40%
Middle back	11	39.30%

Pain regions	Frequency	Percentage
Between shoulder blades	9	32.10%
Sacrum	6	21.40%
Buttocks	6	21.40%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 47 End of treatment week pain quality and rhythm frequency – REA (n=28)

Pain quality	Frequency	Percentage	Pain rhythm	Frequency	Percentage
Sharp	**13**	**46.40%**	**All the time**	**17**	**60.70%**
Burning	**12**	**42.90%**	Fluctuate	9	32.10%
Fixed location	9	32.10%	Worse in the afternoon	9	32.10%
Pricking	9	32.10%	Worse when first get up	9	28.60%
Numbness	9	32.10%	Worse at the end of the day	7	25.00%
Hot	9	32.10%	Worse at night, better during the day	5	17.90%
Moving from one spot to another	7	25.00%	Worse in the morning	4	14.30%
Dull	7	25.00%	Worse during the day, better at night	2	7.10%
Pulling	6	21.40%	*Worse at lunch time*	*1*	*3.60%*
Dull pain with weakness	6	21.40%	*Recurrent*	*0*	*0.00%*
Distending	4	14.30%	*Not known*	*0*	*0.00%*
Cold	3	10.70%			
Not known	*0*	*0.00%*			

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 48 End of treatment week pain aggravator frequency – REA (n=28)

Pain aggravators	Frequency	Percentage
Environmental changes		
Cold weather	**13**	**46.40%**
Weather change	7	25.00%
Hot weather	7	25.00%
Wet weather	3	10.70%
Windy days	*0*	*0.00%*
Exercises or sporting		
Standing	**18**	**64.30%**
Physical work	**17**	**60.70%**
Sitting	**15**	**53.60%**
Lifting	**15**	**53.60%**
Bending	**15**	**53.60%**
Walking	**13**	**46.40%**
Going up/down stairs	**12**	**42.90%**
Driving	8	28.60%

Lying down	7	25.00%
Any movement	6	21.40%
Physiological and psychic changes		
Bad night sleep	**14**	**50.00%**
Stress	**14**	**50.00%**
Being emotional	10	35.70%
After eating	*0*	*0.00%*
Being hungry	*0*	*0.00%*
Others		
Household chores	**12**	**42.90%**
Pressure on the area	10	35.70%
Everything	6	21.40%
Sex	2	7.10%
Not known	2	7.10%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 49 End of treatment week pain alleviator frequency – REA (n=28)

Pain alleviators	Frequency	Percentage
Environmental changes		
Hot packs	**16**	**57.10%**
Warm/hot shower	8	28.60%
Hot weather	7	25.00%
Warm/hot bath	6	21.40%
Cold packs	4	14.30%
Cold weather	3	10.70%
Wet weather	*0*	*0.00%*
Windy days	*0*	*0.00%*
Exercises or sporting		
Resting	**13**	**46.40%**
Gentle exercise	10	35.70%
Lying down	9	32.10%
Gentle massage	9	32.10%
Walking	6	21.40%
Sitting	5	17.90%
Any movement	5	17.90%
Standing	*1*	*3.60%*
Driving	*1*	*3.60%*
Physiological and psychic changes		
Pain killer	**24**	**85.70%**
Keeping my mind off pain	**13**	**46.40%**
Sleep	10	35.70%
Being with other people	9	32.10%
Deep breathing	8	28.60%
Reading	8	28.60%
Watching TV	7	25.00%
Bowel movement	6	21.40%
Pressure on the pain area	4	14.30%
Working	2	7.10%

Pain alleviators	Frequency	Percentage
Eating	*1*	*3.60%*
Belching	*1*	*3.60%*
Being hungry	*0*	*0.00%*
Alcohol	*0*	*0.00%*
Others		
Keeping busy	10	35.70%
Household chores	2	7.10%
Sex	*1*	*3.60%*
Everything	*1*	*3.60%*
Nothing	*0*	*0.00%*
Not known	*0*	*0.00%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 50 End of treatment week other symptom frequency – REA (n=28)

Item	Frequency	Percentage
Feeling tired easily	**17**	**60.70%**
Insomnia	**15**	**53.60%**
Limited movement	**14**	**50.00%**
Night sweating	**13**	**46.40%**
Irritable	**12**	**42.90%**
Poor concentration	**12**	**42.90%**
Poor memory	**12**	**42.90%**
Feeling cold easily	11	39.30%
Feeling hot easily	11	39.30%
Constipation	11	39.30%
Low libido	11	39.30%
Feeling depressed	10	35.70%
Cold hands and feet	9	32.10%
Thirsty	9	32.10%
Sweat upon mild activities	9	32.10%
Frequent urination at night	8	28.60%
Reflux	8	28.60%
Swollen joints	7	25.00%
Indigestion	7	25.00%
Dry skin	7	25.00%
Feeling nervous easily	7	25.00%
Flushed face	6	21.40%
Poor appetite	6	21.40%
Red and hot joints	5	17.90%
Cold joints	5	17.90%
Heavy sensation in the body	5	17.90%
Dry or sore throat	5	17.90%
Hot palms	5	17.90%
Need deep breathing	5	17.90%
Belching	5	17.90%
Nausea	5	17.90%
Dizziness	5	17.90%

Item	Frequency	Percentage
Skin itch	5	17.90%
Leak when sneezing or cough	4	14.30%
Sigh often	4	14.30%
Short of breath	4	14.30%
Abdominal distention	4	14.30%
Catch cold easily	3	10.70%
Distention sensation in the abdomen	2	7.10%
Cold lower back or knees	2	7.10%
Watery diarrhoea	2	7.10%
Frequent urination	2	7.10%
Stuffiness in the chest	2	7.10%
Mushy stools	*1*	*3.60%*
Dry stools	*1*	*3.60%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 51 End of treatment week pain region frequency – SEA (n=23)

Pain regions	Frequency	Percentage
Head and shoulder regions		
Neck	**15**	**65.20%**
Shoulder	**15**	**65.20%**
Shoulder blades	9	39.10%
Back of the head	8	34.80%
Sides of the head	7	30.40%
Frontal head	4	17.40%
Vertex	3	13.00%
Upper limb		
Hand	**10**	**43.50%**
Elbow	9	39.10%
Upper arm	8	34.80%
Fingers	8	34.80%
Wrist	7	30.40%
Forearm	4	17.40%
Lower limb		
Hip	**12**	**52.20%**
Thigh	**12**	**52.20%**
Knee	**12**	**52.20%**
Ankle	8	34.80%
Toes	7	30.40%
Sole	6	26.10%
Front of the leg	5	21.70%
Calf	5	21.70%
Heel	4	17.40%
Front of the body		
Side of the body	8	34.80%
Chest	7	30.40%
Stomach	4	17.40%
Abdomen	2	8.70%

Pain regions	Frequency	Percentage
Groin	2	8.70%
Back of the body		
Lower back	**18**	**78.30%**
Between shoulder blades	**11**	**47.80%**
Middle back	9	39.10%
Buttocks	9	39.10%
Sacrum	4	17.40%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 52 End of treatment week pain quality and rhythm frequency - SEA (n=23)

Pain quality	Frequency	Percentage	Pain rhythm	Frequency	Percentage
Sharp	**12**	**52.20%**	**All the time**	**15**	**65.20%**
Dull pain with weakness	**10**	**43.50%**	**Worse at night, better during the day**	**10**	**43.50%**
Numbness	9	39.10%	Worse at the end of the day	9	39.10%
Dull	8	34.80%	Worse when first get up	8	34.80%
Moving from one spot to another	7	30.40%	Worse in the afternoon	7	30.40%
Pulling	6	26.10%	Worse during the day, better at night	6	26.10%
Fixed location	6	26.10%	Fluctuate	4	17.40%
Cold	5	21.70%	Worse in the morning	4	17.40%
Pricking	5	21.70%	*Worse at lunch time*	*1*	*4.30%*
Burning	5	21.70%	*Recurrent*	*0*	*0.00%*
Hot	3	13.00%	*Not known*	*0*	*0.00%*
Distending	*1*	*4.30%*			
Not known	*1*	*4.30%*			

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 53 End of treatment week pain aggravator frequency – SEA (n=23)

Pain aggravators	Frequency	Percentage
Environmental changes		
Cold weather	**18**	**78.30%**
Weather change	4	17.40%
Hot weather	4	17.40%
Windy days	3	13.00%
Wet weather	2	8.70%
Exercises or sporting		
Physical work	**15**	**65.20%**
Standing	**14**	**60.90%**
Walking	**13**	**56.50%**
Lifting	**13**	**56.50%**

Pain aggravators	Frequency	Percentage
Sitting	**12**	**52.20%**
Bending	**11**	**47.80%**
Going up/down stairs	8	34.80%
Driving	8	34.80%
Lying down	7	30.40%
Any movement	5	21.70%
Physiological and psychic changes		
Bad night sleep	**15**	**65.20%**
Stress	**12**	**52.20%**
Being emotional	8	34.80%
Being hungry	*1*	*4.30%*
After eating	*0*	*0.00%*
Others		
Household chores	**11**	**47.80%**
Pressure on the area	7	30.40%
Everything	5	21.70%
Sex	4	17.40%
Not known	*0*	*0.00%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 54 End of treatment week pain alleviator frequency – SEA (n=23)

Pain alleviators	Frequency	Percentage
Environmental changes		
Hot packs	**18**	**78.30%**
Warm/hot shower	**14**	**60.90%**
Warm/hot bath	7	30.40%
Hot weather	6	26.10%
Cold packs	2	8.70%
Cold weather	*1*	*4.30%*
Wet weather	*0*	*0.00%*
Windy days	*0*	*0.00%*
Exercises or sporting		
Gentle massage	9	39.10%
Resting	9	39.10%
Walking	5	21.70%
Lying down	5	21.70%
Sitting	5	21.70%
Gentle exercise	5	21.70%
Driving	4	17.40%
Any movement	*1*	*4.30%*
Standing	*0*	*0.00%*
Physiological and psychic changes		
Pain killer	**17**	**73.90%**
Keeping my mind off pain	**12**	**52.20%**
Sleep	7	30.40%
Pressure on the pain area	6	26.10%
Reading	6	26.10%

Pain alleviators	Frequency	Percentage
Deep breathing	5	21.70%
Being with other people	4	17.40%
Bowel movement	3	13.00%
Watching TV	3	13.00%
Alcohol	2	8.70%
Being hungry	*1*	*4.30%*
Working	*1*	*4.30%*
Eating	*0*	*0.00%*
Belching	*0*	*0.00%*
Others		
Keeping busy	**10**	**43.50%**
Nothing	4	17.40%
Sex	*1*	*4.30%*
Everything	*1*	*4.30%*
Household chores	*1*	*4.30%*
Not known	*0*	*0.00%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 55 End of treatment week other accompanying symptom frequency – SEA (n=23)

Other symptoms and Frequency	Frequency	Percentage
Feeling tired easily	**19**	**82.60%**
Poor concentration	**13**	**56.50%**
Limited movement	**12**	**52.20%**
Feeling nervous easily	**12**	**52.20%**
Feeling depressed	**12**	**52.20%**
Feeling cold easily	**11**	**47.80%**
Irritable	**11**	**47.80%**
Poor memory	**11**	**47.80%**
Thirsty	**10**	**43.50%**
Cold hands and feet	9	39.10%
Insomnia	9	39.10%
Constipation	9	39.10%
Dry or sore throat	8	34.80%
Feeling hot easily	7	30.40%
Night sweating	7	30.40%
Need deep breathing	7	30.40%
Short of breath	7	30.40%
Swollen joints	6	26.10%
Heavy sensation in the body	6	26.10%
Dry skin	6	26.10%
Sweat upon mild activities	6	26.10%
Red and hot joints	5	21.70%
Cold joints	5	21.70%
Frequent urination at night	5	21.70%
Catch cold easily	5	21.70%
Stuffiness in the chest	5	21.70%

Other symptoms and Frequency	Frequency	Percentage
Skin itch	5	21.70%
Indigestion	4	17.40%
Cold lower back or knees	4	17.40%
Flushed face	4	17.40%
Frequent urination	4	17.40%
Sigh often	4	17.40%
Reflux	4	17.40%
Dizziness	4	17.40%
Leak when sneezing or cough	3	13.00%
Low libido	3	13.00%
Poor appetite	3	13.00%
Distention sensation in the abdomen	2	8.70%
Abdominal distention	2	8.70%
Nausea	2	8.70%
Watery diarrhoea	*1*	*4.30%*
Mushy stools	*1*	*4.30%*
Dry stools	*1*	*4.30%*
Belching	*1*	*4.30%*
Hot palms	*0*	*0.00%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 56 End of treatment week pain region frequency – PMM alone (n=17)

Pain regions	Frequency	Percentage
Head and shoulder regions		
Shoulder	**7**	**41.20%**
Neck	5	29.40%
Shoulder blades	5	29.40%
Frontal head	3	17.60%
Sides of the head	3	17.60%
Back of the head	3	17.60%
Vertex	1	5.90%
Upper limb		
Upper arm	4	23.50%
Wrist	4	23.50%
Fingers	4	23.50%
Hand	2	11.80%
Elbow	1	5.90%
Forearm	1	5.90%
Lower limb		
Knee	**9**	**52.90%**
Hip	**7**	**41.20%**
Thigh	**7**	**41.20%**
Front of the leg	**7**	**41.20%**
Calf	**7**	**41.20%**
Toes	6	35.30%
Ankle	4	23.50%
Heel	4	23.50%

Pain regions	Frequency	Percentage
Sole	4	23.50%
Front of the body		
Groin	4	23.50%
Stomach	2	11.80%
Chest	1	5.90%
Abdomen	1	5.90%
Side of the body	1	5.90%
Back of the body		
Lower back	**15**	**88.20%**
Between shoulder blades	**4**	**41.20%**
Sacrum	**7**	**41.20%**
Middle back	6	35.30%
Buttocks	5	29.40%

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 57 End of treatment week pain quality and rhythm frequency – PMM alone (n=17)

Pain quality	Frequency	Percentage	Pain rhythm	Frequency	Percentage
Sharp	**11**	**64.70%**	**All the time**	**11**	**64.70%**
Fixed location	**8**	**47.10%**	**Worse at the end of the day**	**7**	**41.20%**
Burning	**7**	**41.20%**	Worse when first get up	5	29.40%
Dull	6	35.30%	Fluctuate	4	23.50%
Pricking	3	17.60%	Worse at night, better during the day	4	23.50%
Numbness	3	17.60%	Worse during the day, better at night	3	17.60%
Dull pain with weakness	3	17.60%	Worse in the afternoon	3	17.60%
Cold	2	11.80%	Worse in the morning	2	11.80%
Pulling	2	11.80%	Recurrent	1	5.90%
Moving from one spot to another	2	11.80%	Not known	1	5.90%
Hot	2	11.80%	*Worse at lunch time*	*0*	*0.00%*
Distending	1	5.90%			
Not known	*0*	*0.00%*			

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 58 End of treatment week pain aggravator frequency – PMM alone (n=17)

Pain aggravators	Frequency	Percentage
Environmental changes		
Cold weather	**13**	**76.50%**
Wet weather	4	23.50%
Weather change	4	23.50%
Windy days	3	17.60%

Pain aggravators	Frequency	Percentage
Hot weather	2	11.80%
Exercises or sporting		
Standing	**13**	**76.50%**
Walking	**11**	**64.70%**
Physical work	**10**	**58.80%**
Lifting	**10**	**58.80%**
Going up/down stairs	**10**	**58.80%**
Sitting	**8**	**47.10%**
Bending	**8**	**47.10%**
Driving	6	35.30%
Lying down	3	17.60%
Any movement	2	11.80%
Physiological and psychic changes		
Bad night sleep	**7**	**41.20%**
Stress	6	35.30%
Being emotional	5	29.40%
After eating	1	5.90%
Being hungry	1	5.90%
Others		
Household chores	**8**	**47.10%**
Pressure on the area	4	23.50%
Everything	4	23.50%
Sex	3	17.60%
Not known	*0*	*0.00%*

Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 59 End of treatment week pain alleviator frequency – PMM alone (n=17)

Pain alleviators	Frequency	Percentage
Environmental changes		
Hot packs	**11**	**64.70%**
Warm/hot shower	**9**	**52.90%**
Hot weather	3	17.60%
Warm/hot bath	3	17.60%
Cold packs	2	11.80%
Cold weather	*0*	*0.00%*
Wet weather	*0*	*0.00%*
Windy days	*0*	*0.00%*
Exercises or sporting		
Lying down	**7**	**41.20%**
Resting	**7**	**41.20%**
Gentle massage	6	35.30%
Gentle exercise	4	23.50%
Sitting	3	17.60%
Any movement	1	5.90%
Driving	1	5.90%
Standing	*0*	*0.00%*
Walking	*0*	*0.00%*

Pain alleviators	Frequency	Percentage
Physiological and psychic changes		
Pain killer	**17**	**100.00%**
Keeping my mind off pain	6	35.30%
Sleep	5	29.40%
Deep breathing	3	17.60%
Bowel movement	3	17.60%
Being with other people	3	17.60%
Reading	3	17.60%
Watching TV	3	17.60%
Belching	1	5.90%
Pressure on the pain area	1	5.90%
Alcohol	1	5.90%
Eating	*0*	*0.00%*
Being hungry	*0*	*0.00%*
Working	*0*	*0.00%*
Others		
Keeping busy	4	23.50%
Nothing	3	17.60%
Sex	2	11.80%
Everything	*0*	*0.00%*
Household chores	*0*	*0.00%*
Not known	*0*	*0.00%*

Items greater than 40% were bolded and items less than 5% were italicised.

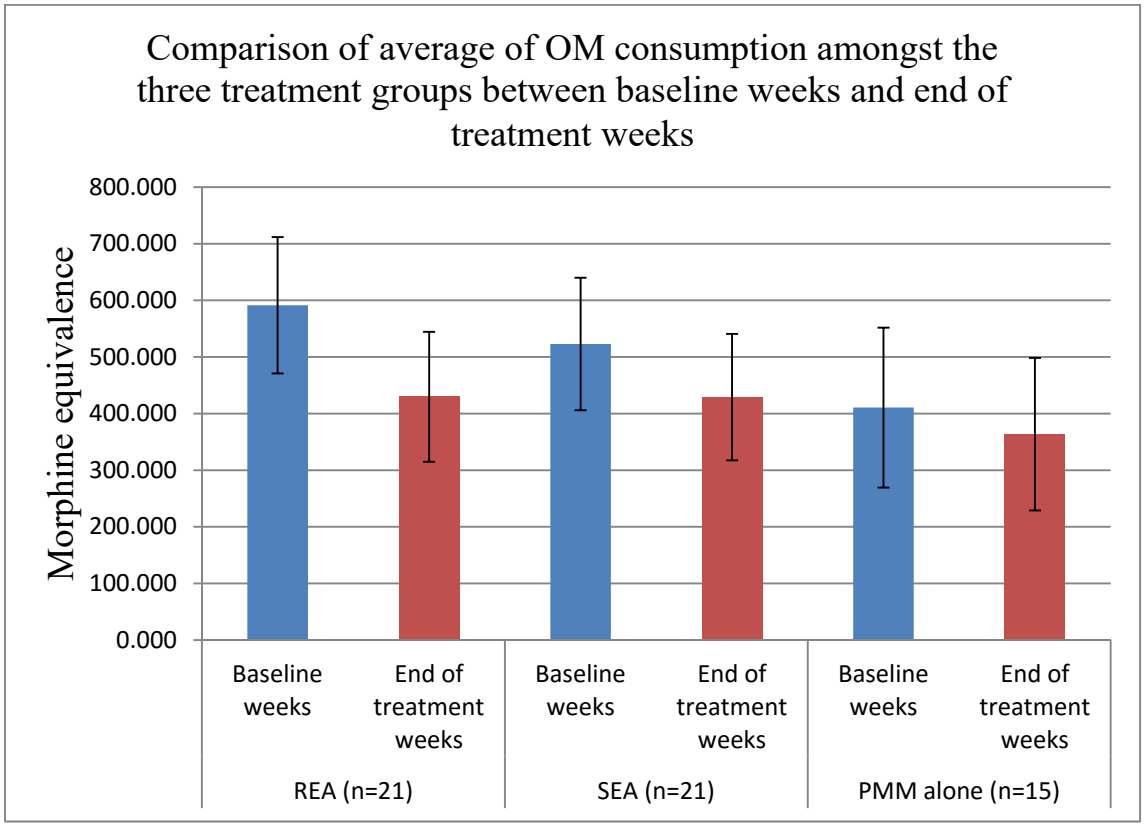
Appendix 60 End of treatment week other pain accompanying symptom frequency – PMM alone (n=17)

Other symptoms	Frequency	Percentage
Feeling tired easily	**11**	**64.70%**
Insomnia	**9**	**52.90%**
Irritable	**9**	**52.90%**
Poor concentration	**9**	**52.90%**
Limited movement	**8**	**47.10%**
Poor memory	**8**	**47.10%**
Low libido	**8**	**47.10%**
Feeling depressed	**8**	**47.10%**
Feeling cold easily	**7**	**41.20%**
Night sweating	**7**	**41.20%**
Constipation	**7**	**41.20%**
Feeling hot easily	6	35.30%
Sweat upon mild activities	6	35.30%
Feeling nervous easily	6	35.30%
Dry skin	5	29.40%
Poor appetite	5	29.40%
Dizziness	5	29.40%
Swollen joints	4	23.50%
Flushed face	4	23.50%
Frequent urination at night	4	23.50%

Other symptoms	Frequency	Percentage
Frequent urination	4	23.50%
Cold joints	3	17.60%
Cold hands and feet	3	17.60%
Dry or sore throat	3	17.60%
Hot palms	3	17.60%
Watery diarrhoea	3	17.60%
Sigh often	3	17.60%
Need deep breathing	3	17.60%
Short of breath	3	17.60%
Cold lower back or knees	2	11.80%
Thirsty	2	11.80%
Leak when sneezing or cough	2	11.80%
Reflux	2	11.80%
Nausea	2	11.80%
Red and hot joints	1	5.90%
Heavy sensation in the body	1	5.90%
Mushy stools	1	5.90%
Dry stools	1	5.90%
Catch cold easily	1	5.90%
Stuffiness in the chest	1	5.90%
Skin itch	1	5.90%
Distention sensation in the abdomen	*0*	*0.00%*
Indigestion	*0*	*0.00%*
Abdominal distention	*0*	*0.00%*
Belching	*0*	*0.00%*

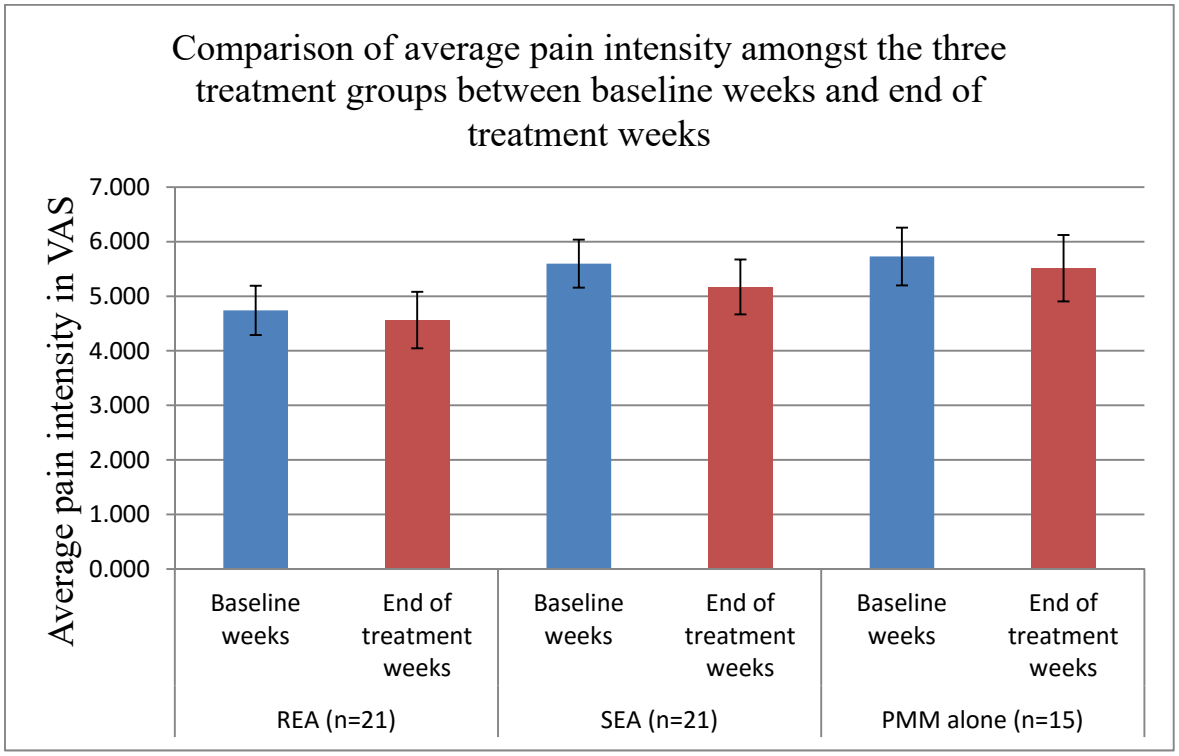
Items greater than 40% were bolded and items less than 5% were italicised.

Appendix 61 Average OM consumption amongst REA, SEA, and PMM alone before and after treatment



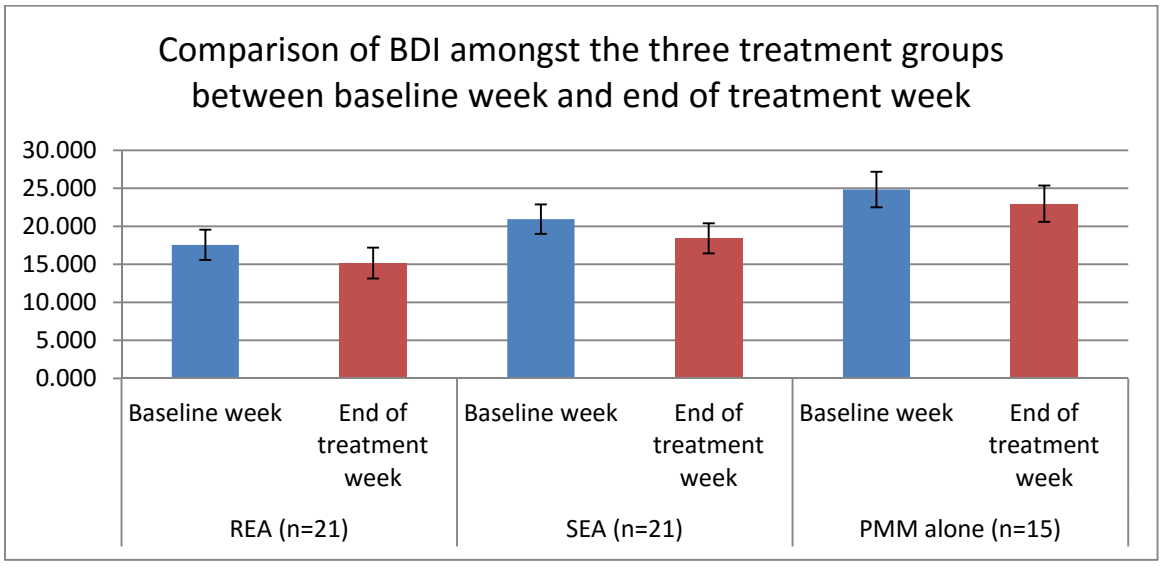
REA: Baseline weeks: Mean: 591.353. Standard error: 120.406. End of treatment weeks: Mean: 429.575. Standard error: 114.826.
SEA: Baseline weeks: Mean: 522.949. Standard error: 117.076. End of treatment weeks: Mean: 429.113. Standard error: 111.651.
PMM alone: Baseline weeks: Mean: 410.699. Standard error: 141.222. End of treatment weeks: Mean: 363.653. Standard error: 134.678.
*p=0.000

Appendix 62 Average pain intensity amongst REA, SEA, and PMM alone before and after treatment



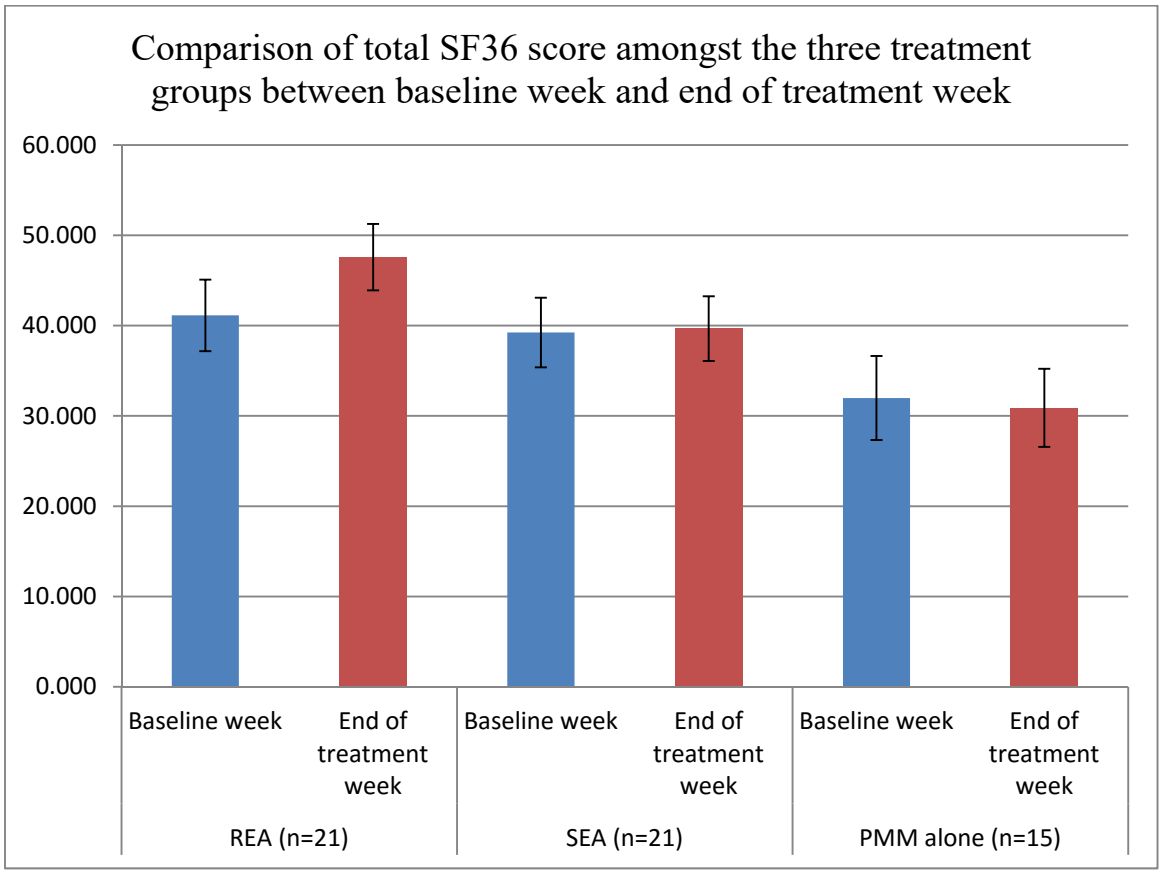
REA: Baseline weeks: Mean: 4.740. Standard error: 0.452. End of treatment weeks: Mean: 4.563. Standard error: 0.518.
SEA: Baseline weeks: Mean: 5.598. Standard error: 0.439. End of treatment weeks: Mean: 5.170. Standard error: 0.504.
PMM alone: Baseline weeks: Mean: 5.728. Standard error: 0.530. End of treatment weeks: Mean: 5.514. Standard error: 0.608.
p=0.144

Appendix 63 Total BDI score amongst REA, SEA, and PMM alone before and after treatment



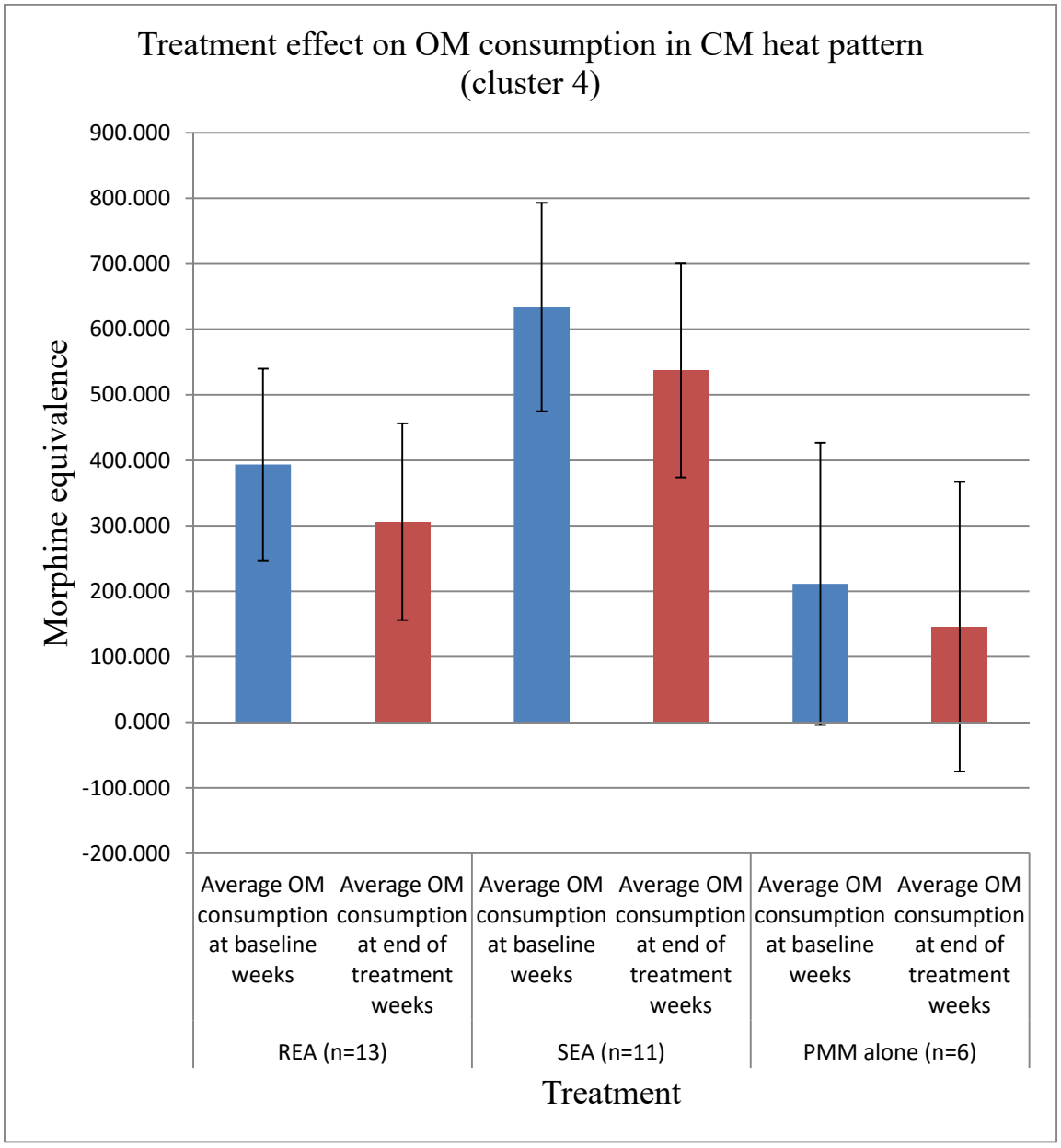
REA: Baseline weeks: Mean: 17.558. Standard error: 1.991. End of treatment weeks: Mean: 15.168. Standard error: 2.034.
SEA: Baseline weeks: Mean: 20.950. Standard error: 1.936. End of treatment weeks: Mean: 18.423. Standard error: 1.978.
PMM alone: Baseline weeks: Mean: 24.833. Standard error: 2.335. End of treatment weeks: Mean: 22.972. Standard error: 2.386.
*p=0.009

Appendix 64 Total SF36 score amongst REA, SEA, and PMM alone before and after treatment



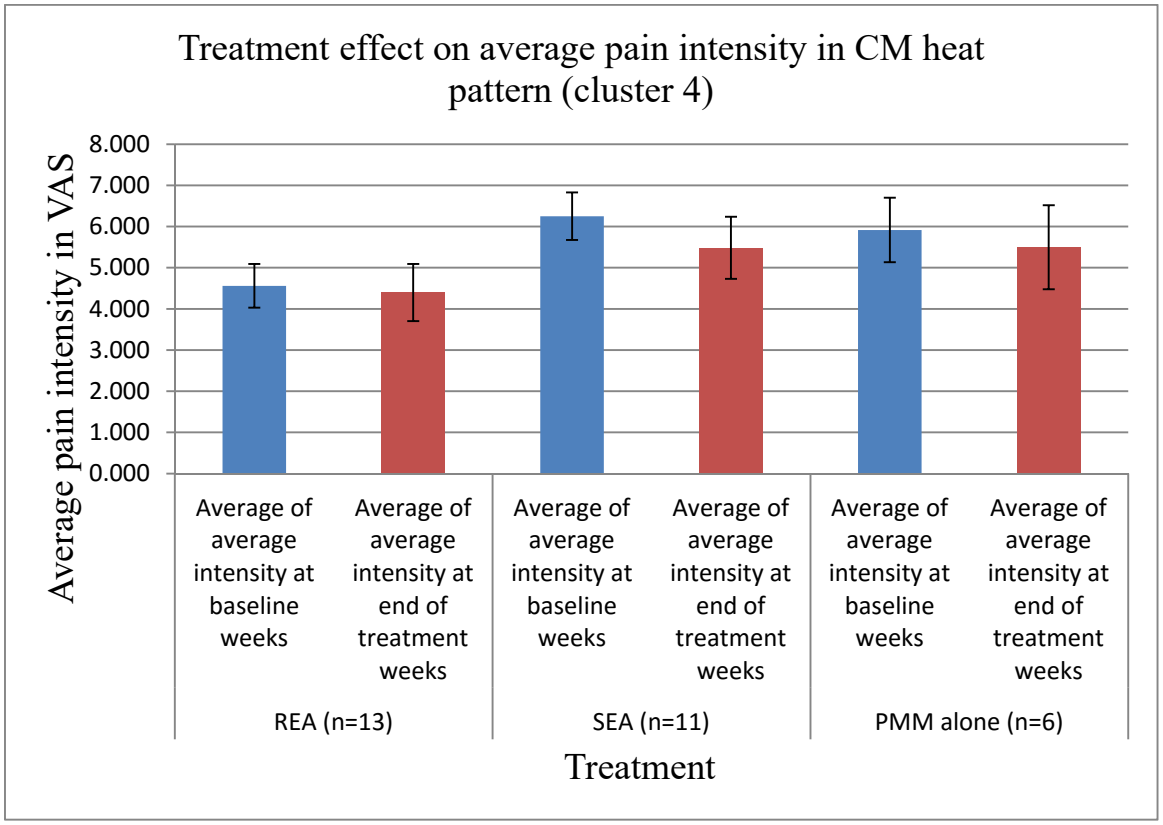
REA: Baseline weeks: Mean: 41.131. Standard error: 3.968. End of treatment weeks: Mean: 47.577. Standard error: 3.682.
SEA: Baseline weeks: Mean: 39.238. Standard error: 3.858. End of treatment weeks: Mean: 39.659. Standard error: 3.580.
PMM alone: Baseline weeks: Mean: 31.983. Standard error: 4.654. End of treatment weeks: Mean: 30.896. Standard error: 4.318.
p=0.284

Appendix 65 Average OM consumption amongst REA, SEA, and PMM alone before and after treatment – cluster 4



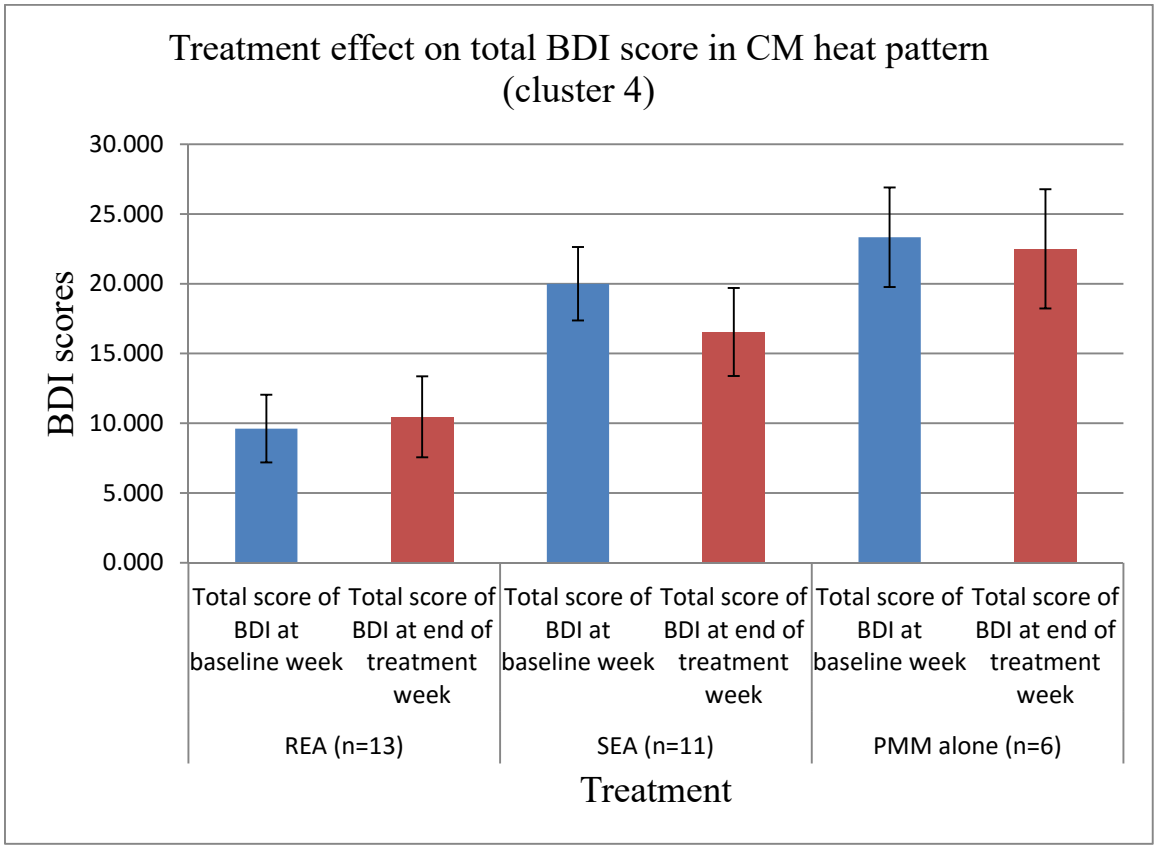
REA: Baseline weeks: Mean: 393.5223. Standard error: 96.96596. End of treatment weeks: Mean: 306.1061. Standard error: 99.27312.
SEA: Baseline weeks: Mean: 633.9922. Standard error: 231.36724. End of treatment weeks: Mean: 537.0635. Standard error: 236.75248.
PMM alone: Baseline weeks: Mean: 211.3896. Standard error: 73.66412. End of treatment weeks: Mean: 145.9207. Standard error: 84.27099.
p=0.802
CM: Chinese medicine
PMM alone: Pain medication management alone
OM: Opioid medication
REA: Real electro acupuncture
SEA: Sham electro acupuncture

Appendix 66 Average pain intensity amongst REA, SEA, and PMM alone before and after treatment – cluster 4



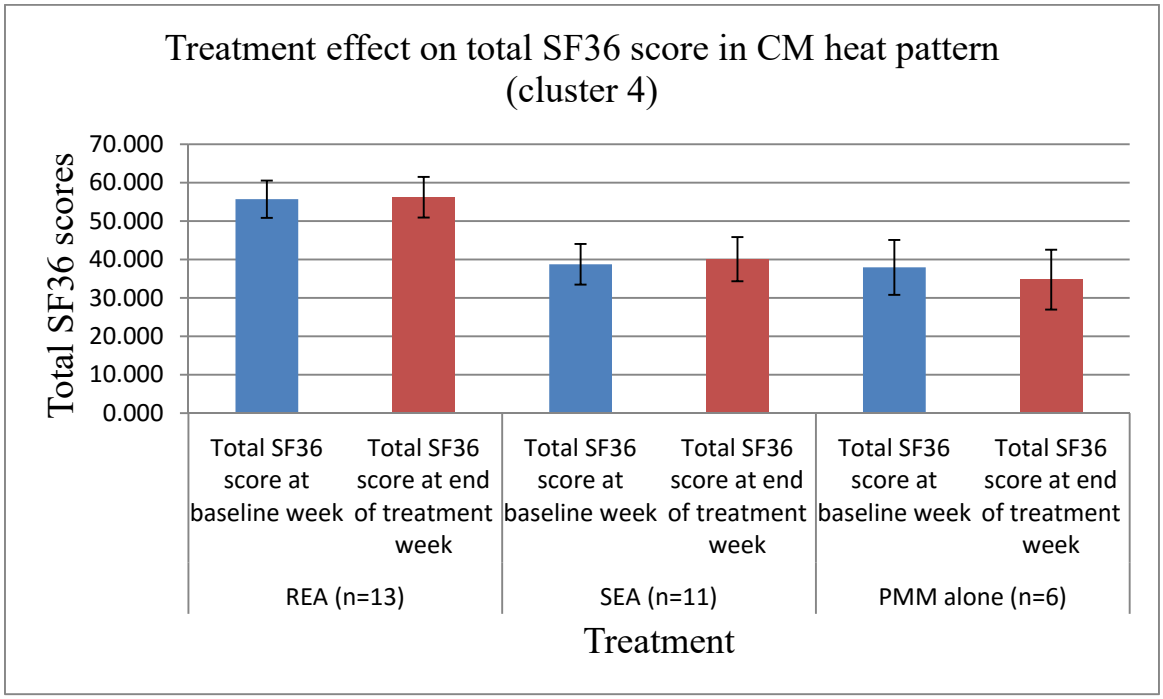
REA: Baseline weeks: Mean: 4.5593. Standard error: 0.55864. End of treatment weeks: Mean: 4.3973. Standard error: 0.74371.
SEA: Baseline weeks: Mean: 6.2510. Standard error: 0.50255. End of treatment weeks: Mean: 5.4831. Standard error: 0.66731.
PMM alone: Baseline weeks: Mean: 5.9167. Standard error: 0.86739. End of treatment weeks: Mean: 5.4976. Standard error: 1.05552.
p=0.649
CM: Chinese medicine
PMM alone: Pain medication management alone
REA: Real electro acupuncture
SEA: Sham electro acupuncture
VAS: Visual analogue scale

Appendix 67 Total BDI score amongst REA, SEA, and PMM alone before and after treatment – cluster 4



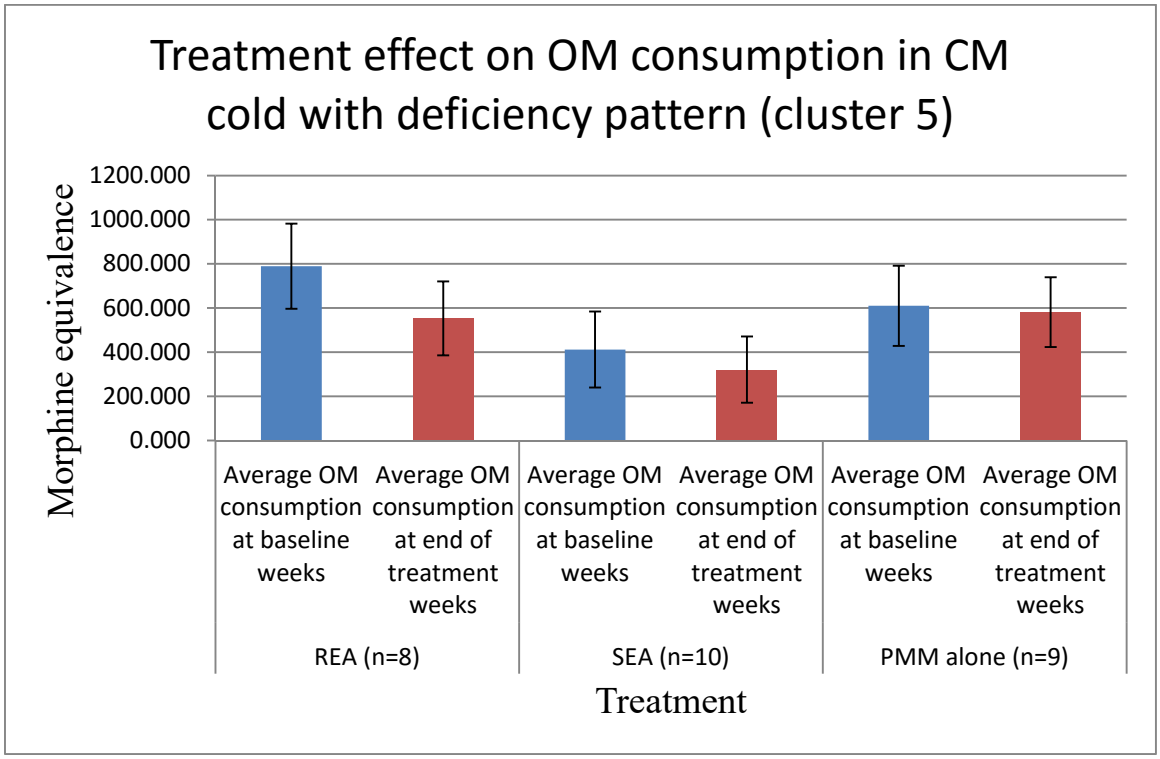
REA: Baseline weeks: Mean: 9.6154. Standard error: 1.94652. End of treatment weeks: Mean: 10.4615. Standard error: 2.28320.
SEA: Baseline weeks: Mean: 20.0000. Standard error: 2.01810. End of treatment weeks: Mean: 16.5455. Standard error: 2.00619.
PMM alone: Baseline weeks: Mean: 23.3333. Standard error: 5.84618. End of treatment weeks: Mean: 22.5000. Standard error: 7.52662.
p=0.189
BDI: Beck depression inventory
CM: Chinese medicine
PMM alone: Pain medication management alone
REA: Real electro acupuncture
SEA: Sham electro acupuncture

Appendix 68 Total SF36 score amongst REA, SEA, and PMM alone before and after treatment – cluster 4



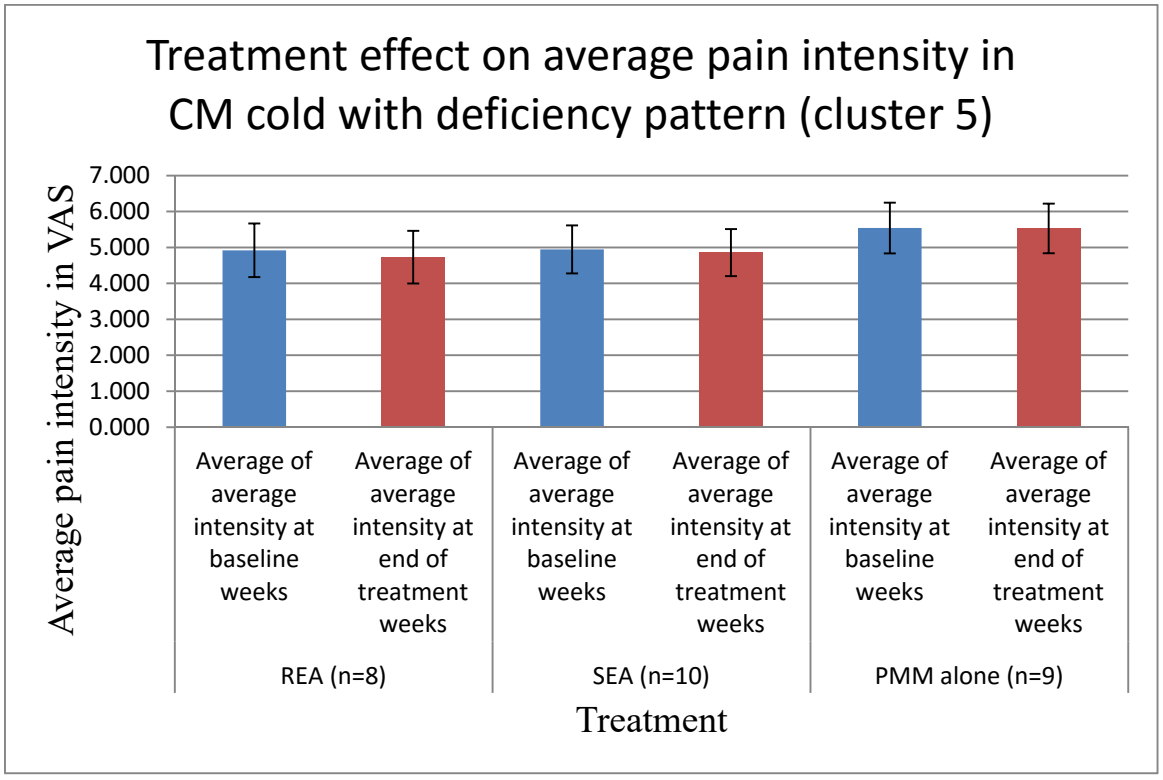
REA: Baseline weeks: Mean: 55.6907. Standard error: 4.75574. End of treatment weeks: Mean: 56.1955. Standard error: 5.25455.
SEA: Baseline weeks: Mean: 38.7595. Standard error: 4.38211. End of treatment weeks: Mean: 40.0909. Standard error: 4.81189.
PMM alone: Baseline weeks: Mean: 37.9410. Standard error: 9.40913. End of treatment weeks: Mean: 34.7569. Standard error: 9.95014.
p=0.773
CM: Chinese medicine
PMM alone: Pain medication management alone
REA: Real electro acupuncture
SEA: Sham electro acupuncture
SF36: Medical outcome short form health survey 36 items

Appendix 69 OM consumption amongst REA, SEA, and PMM alone before and after treatment – cluster 5



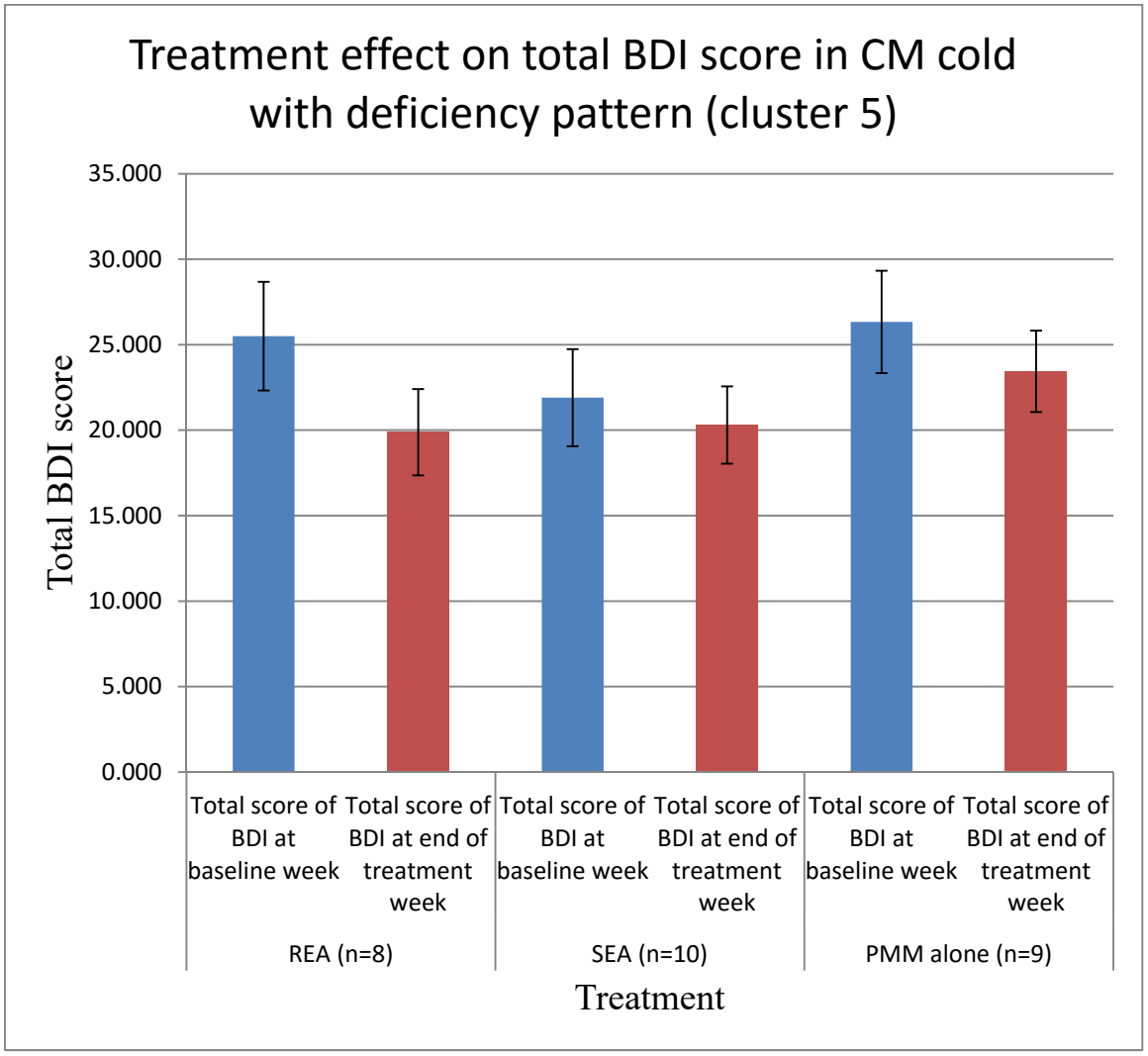
REA: Baseline weeks: Mean: 789.1844. Standard error: 236.47300. End of treatment weeks: Mean: 553.0438. Standard error: 218.59999.
SEA: Baseline weeks: Mean: 411.9060. Standard error: 73.16018. End of treatment weeks: Mean: 321.1634. Standard error: 71.41975.
PMM alone: Baseline weeks: Mean: 610.0077. Standard error: 220.96726. End of treatment weeks: Mean: 581.3856. Standard error: 77.54145.
p=0.168
CM: Chinese medicine
PMM alone: Pain medication management alone
OM: Opioid medication
REA: Real electro acupuncture
SEA: Sham electro acupuncture

Appendix 70 Average pain intensity amongst REA, SEA, and PMM alone before and after treatment – cluster 5



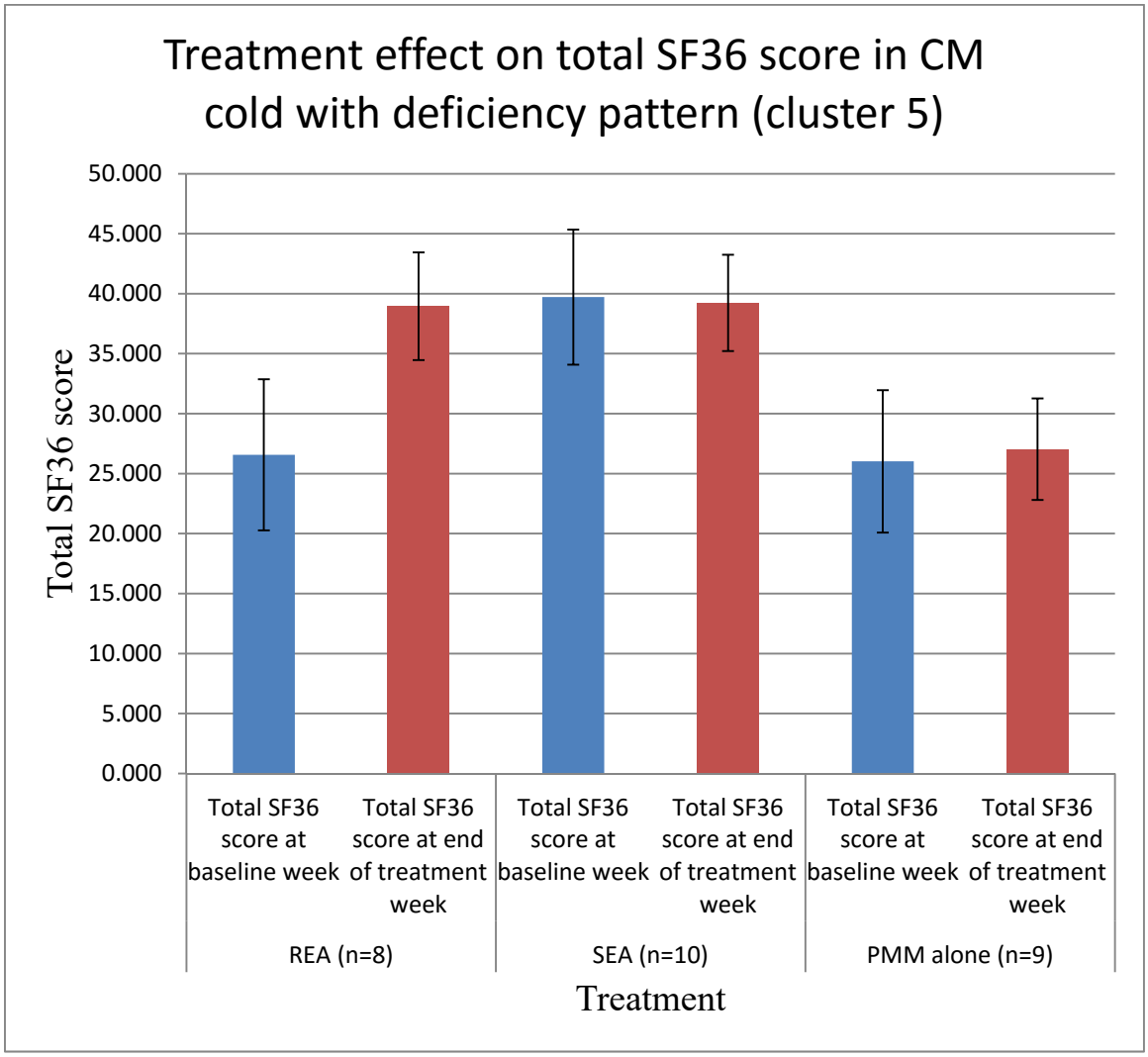
REA: Baseline weeks: Mean: 4.9205. Standard error: 0.52584. End of treatment weeks: Mean: 4.7281. Standard error: 0.50900.
SEA: Baseline weeks: Mean: 4.9443. Standard error: 0.82533. End of treatment weeks: Mean: 4.8568. Standard error: 0.71616.
PMM alone: Baseline weeks: Mean: 5.5397. Standard error: 0.64878. End of treatment weeks: Mean: 5.5302. Standard error: 0.76502.
p=0.935
CM: Chinese medicine
PMM alone: Pain medication management alone
REA: Real electro acupuncture
SEA: Sham electro acupuncture
VAS: Visual analogue scale

Appendix 71 Total BDI score amongst REA, SEA, and PMM alone before and after treatment – cluster 5



REA: Baseline weeks: Mean: 25.5000. Standard error: 3.59563. End of treatment weeks: Mean: 19.8750. Standard error: 3.08474.
SEA: Baseline weeks: Mean: 21.9000. Standard error: 2.89233. End of treatment weeks: Mean: 20.3000. Standard error: 2.17077.
PMM alone: Baseline weeks: Mean: 26.3333. Standard error: 2.53311. End of treatment weeks: Mean: 23.4444. Standard error: 1.93011.
p=0.450
BDI: Beck depression inventory
CM: Chinese medicine
PMM alone: Pain medication management alone
REA: Real electro acupuncture
SEA: Sham electro acupuncture

Appendix 72 Total SF36 score amongst REA, SEA, and PMM alone before and after treatment – cluster 5



REA: Baseline weeks: Mean: 26.5703. Standard error: 7.89021. End of treatment weeks: Mean: 38.9583. Standard error: 4.38784.
SEA: Baseline weeks: Mean: 39.7167. Standard error: 6.46276. End of treatment weeks: Mean: 39.2271. Standard error: 5.24358.
PMM alone: Baseline weeks: Mean: 26.0255. Standard error: 2.24997. End of treatment weeks: Mean: 27.0347. Standard error: 2.10140.
p=0.118
CM: Chinese medicine
PMM alone: Pain medication management alone
REA: Real electro acupuncture
SEA: Sham electro acupuncture
SF36: Medical outcome short form health survey 36 items